UNIVERSITY OF ALBERTA

Radical Cyclization Routes to Propellanes and Bicyclic Lactones Related to Prostaglandins

by

Darrin L. Mayhew ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Radical Cyclization Routes to Propellanes and Bicyclic Lactones Related to Prostaglandins** submitted by **Darrin L. Mayhew** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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To my family

ABSTRACT

The first part of this thesis describes radical cyclization routes to propellanes. The propellane system, while not common in nature, is present in a few sesquiterpene natural products. Both enyne radical closures, and radical closures based on epoxides, were examined, with the epoxide route being more efficient at generating the propellanes. This work has been published (*J. Org. Chem.* **1996**, *61*, 2095).

In part 2, the application of a tandem radical cyclization route to prostaglandin intermediates is described. Both the Corey lactone and 11-deoxy Corey lactone were synthesized.

The tandem cyclization involves a 5-*exo*-*trig* radical closure, followed by a 1,5-hydrogen abstraction, and 5-*endo*-*dig* radical closure. The result is the formation of cyclopentane rings, with good stereocontrol of the ring substituents.

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LIST OF ABBREVIATIONS

AIBN.....2,2'-azobisisobutyronitrile

APT.....attached proton test

Bn.....benzyl

Bu.....butyl

t-Bu.....*tert*-butyl

Cp.....cyclopentadienyl

m-CPBA.....*m*-chloroperoxybenzoic acid

DIB.....(diacetoxyiodo)benzene

DIBAL.....diisobutylaluminum hydride

DMAP.....4-(dimethylamino)pyridine

DMF.....dimethylformamide

DMSO.....dimethyl sulfoxide

HMPA.....hexamethylphosphoric triamide

Hz.....hertz

KHMDS.....potassium hexamethyldisilazide

LAH.....lithium aluminum hydride

LDA.....lithium diisopropylamide

LDBB.....lithium 4,4'-di-*tert*-butylbiphenyl

MEM.....methoxyethoxymethyl

MOM.....methoxymethyl

MS.....mass spectrometry

NIS.....*N*-iodosuccinimide

NMO.....4-methylmorpholine *N*-oxide

NMR.....nuclear magnetic resonance

NOE.....nuclear Overhauser enhancement

PCC.....pyridinium chlorochromate

PG.....prostaglandin

Ph.....phenyl

Piv.....trimethylacetyl (pivaloyl)

PPA.....polyphosphoric acid

PPTS.....pyridinium *p*-toluenesulfonate

PRT.....protecting/radical translocating

TBAF.....tetrabutylammonium fluoride

TBDMS.....*tert*-butyldimethylsilyl

TBDPS.....*tert*-butyldiphenylsilyl

TES.....triethylsilyl

THF.....tetrahydrofuran

THP.....tetrahydropyran

TLC.....thin layer chromatography

TMS.....trimethylsilyl

TRIBAL.....triisobutylaluminum

TsOH.....*p*-toluenesulfonic acid

CHAPTER 1 - INTRODUCTION

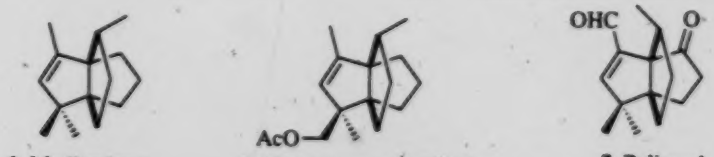
1. General

Propellanes are compounds containing, as part of their structure, a tricyclic system in which all three rings share two common carbon atoms. This property of shared carbon atoms imposes a unique architecture on the system (Figure I-1). The shape is reminiscent of a propeller; hence, the term, propellane, has become established in the literature.

a [3.3.3]propellane a [4.4.3]propellane

Figure I-1 - General Structure and Nomenclature of Propellanes

To distinguish between various ring sizes, the compounds are often named as [m.n.o]propellanes, in which m, n, and o represent the number of non-shared carbon atoms in each of the three rings (Figure I-1). Unlike the related linear and angular triquinanes, the propellane system is not very prevalent in nature and, to date, the [3.3.3] type is the only propellane system that has been observed in natural products (Figure I-2).[1]



1 Modhephene 2 13-Acetoxymodhephene 3 Pulicaral

Figure I-2 - Some propellane-based natural products

The subject of propellanes has been reviewed before[2] (including a book devoted entirely to the subject). The scope of these reviews has been broad, covering such specific topics as small-ring propellanes, heterocyclic systems, and molecular orbital studies of the compounds. The present overview of the literature will deal with the various approaches that have been adopted for the synthesis of larger sized carbocyclic propellanes (where m, n, o are greater than or equal to 3). From a synthetic organic chemistry point of view, these larger propellanes have received the most attention. A further note is that, due to the interest in synthesizing natural products, many of the demonstrated approaches have been introduced in an effort to make one or more of the natural products shown in Figure I-2.

An examination of the literature that deals with propellane synthesis reveals three general strategies that have been used to prepare these compounds:

a) Sequential construction of each ring

b) Tandem processes, in which the propellane skeleton can be constructed in one step from monocyclic compounds

c) Rearrangements, in which a pre-assembled ring system is converted to a propellane by a rearrangement or a series of rearrangements.

2. Sequential Construction of each Ring

Perhaps the simplest approach, conceptually, to propellanes is the initial construction of a bicyclic system (containing a suitable tether) followed by formation of the third ring. This approach is demonstrated in Figure I-3, in which the final ring is completed by joining the appropriate carbon atoms (indicated with an asterisk).

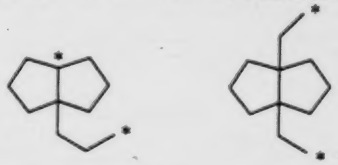
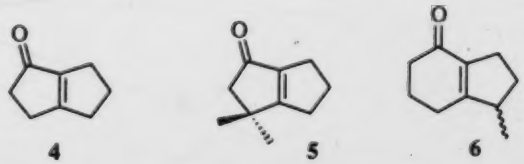


Figure I-3 - Sequential Construction of Propellanes

Partly because of the numerous methods available for making bicyclic compounds of the type shown in Figure I-3, this strategy is the one that is most often reported in the literature.

One family of compounds in particular (Figure I-4) is especially suitable for the purpose of propellane synthesis by this strategy.

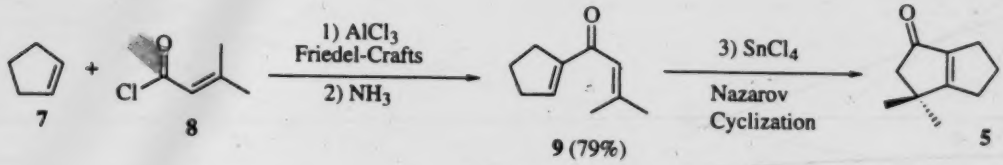


4 5 6

Figure I-4 - Some Bicyclic Enones used for Propellane Synthesis

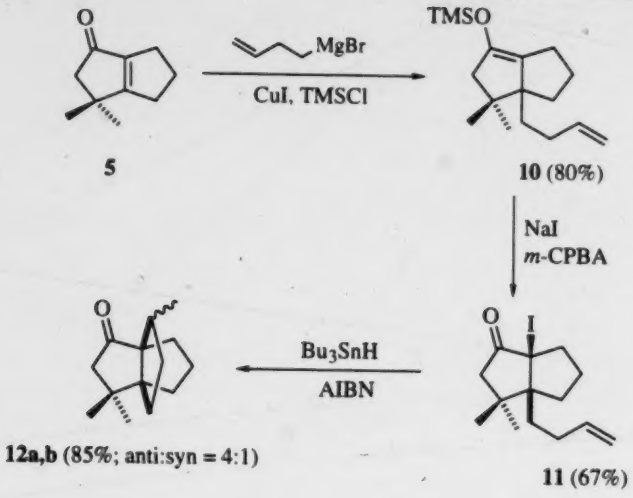
These types of bicyclic ketones have several desirable characteristics that one can take advantage of. First of

all, they are readily available by a variety of methods;[3] a selected example[3c] is shown in Scheme 1. Secondly, the position of the double bond of the enone unit is such that a suitable appendage can be added (for example, via Michael addition) in the correct position for eventual formation of the third ring. Finally, the carbonyl functionality that is present provides a site for further reactions if required. Several of the examples of propellane syntheses that will be presented make use of these bicyclic ketones.



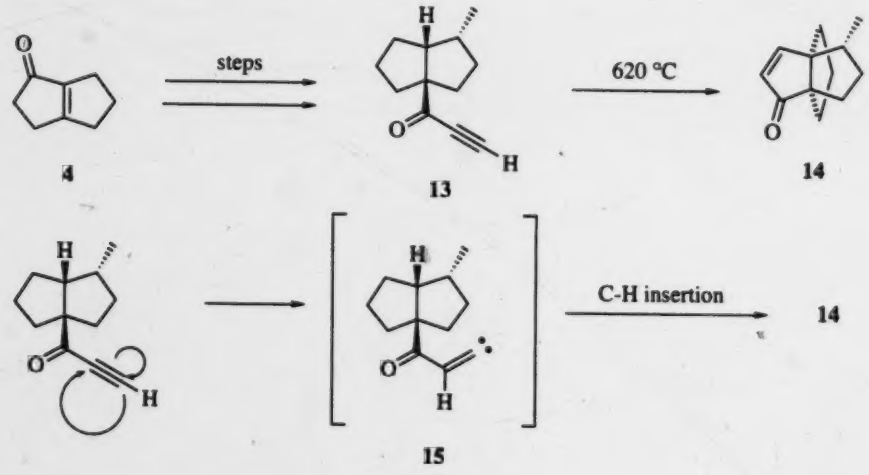
Scheme 1

Sha and co-workers have employed a radical cyclization approach in a propellane synthesis (Scheme 2).[4] Their starting material was the readily available bicyclic enone **5**. Grignard addition, mediated by CuI, followed by enolate trapping with chlorotrimethylsilane, gave **10** in good yield. The silyl enol ether was then converted into a suitable radical precursor in the form of an α-iodo ketone (**10** → **11**). Radical cyclization then took place in a 5-*exo* fashion to generate isomeric propellanes **12a**,**b**.



Scheme 2

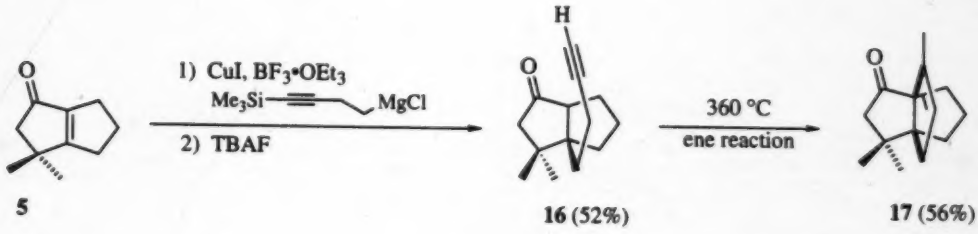
Scheme 3 summarizes an example[5] in which enone **4** is used as the starting material. Compound **13**, available in several steps from **4**, was employed in a thermal α-alkynone cyclization to give propellane **14**.



Scheme 3

The proposed mechanism involves insertion of an alkylidene carbene into the tertiary C-H bond of the diquinane (**15** → **14**). Angular triquinanes were also produced in the reaction as minor products, indicating that insertion into secondary C-H bonds is a competing process.

Similar high temperature reactions have also been used by other groups to construct propellane skeletons. In a procedure developed by Paquette (Scheme 4),[6] enone **5** was converted by standard methods into acetylene **16**, which then underwent a thermal cyclization to generate propellane **17** in reasonable yield. The author proposed an ene reaction mechanism for the transformation, **16** → **17**, but no evidence confirming this process was given. An enantioselective version of Paquette's work was completed by Mash several years later (Scheme 5).[7]

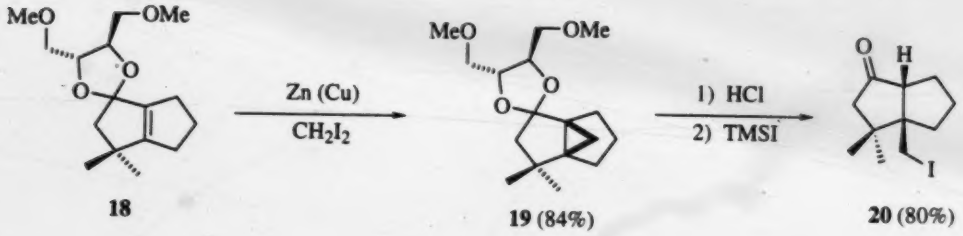


5 **16** (52%) **17** (56%)

Scheme 4

Enantioselective cyclopropanation (directed by the chiral acetal) of **18** afforded **19**, which is classified as a [3.3.1]propellane (Scheme 5). Hydrolysis of the acetal and regioselective opening of the cyclopropane ring produced **20** as a single enantiomer. Further elaboration of **20** eventually

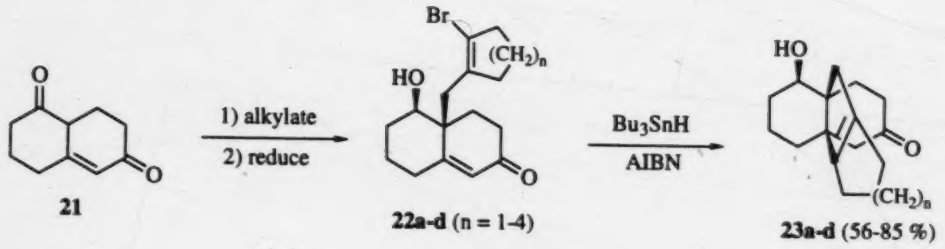
gave the enantiomerically pure version of Paquette's compound **16**. Conversion to the propellane proceeded as in the earlier example with a similar yield reported. Along with these two examples, high temperature cyclizations have also been used by other groups in a similar manner to make propellanes.[8]



18 **19** (84%) **20** (80%)

Scheme 5

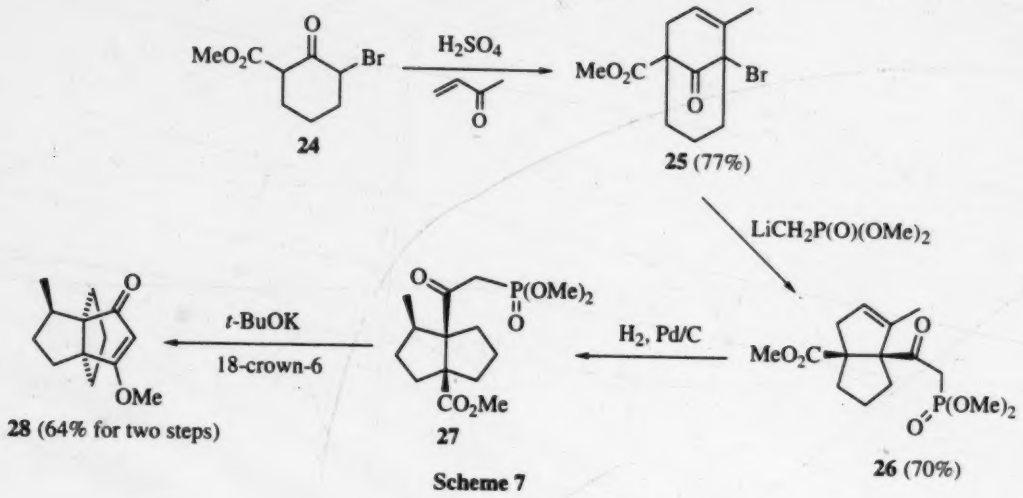
Rajamannar and co-workers have employed compound **21** in the synthesis of a series of [4.4.n]propellanes **23a-d** (Scheme 6).[9]



21 **22a-d** (n = 1-4) **23a-d** (56-85 %)

Scheme 6

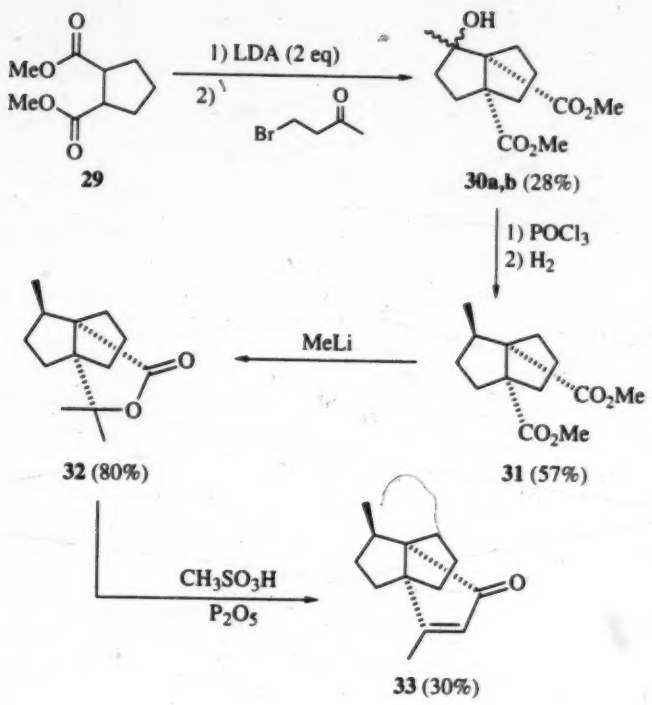
Compounds **22a-d** were available from **21** by a simple two-step procedure of alkylation and reduction. The vinyl radicals derived from **22a-d** then added in a 5-*exo* Michael fashion to the enone moiety to give the desired propellanes **23a-d**.



Scheme 7

Interestingly, the hydroxyl group in compounds **22a-d** is necessary for good yields; a ketone at this position caused 5-*exo* radical closure onto this carbonyl unit to become a competing process.

Kraus has used a clever strategy for making a bicyclic system suitable for eventual propellane formation (Scheme 7).[10] Michael addition of compound **24** to methyl vinyl ketone, followed by aldol condensation, gave bicyclic compound **25**. A tandem sequence of lithiophosphonate addition, followed by ring fragmentation, was then employed to produce ketophosphonate **26**. The substituents at the ring junctions are then used in a Horner-Emmons-type reaction to produce a vinylogous ester-containing propellane (**27** → **28**).

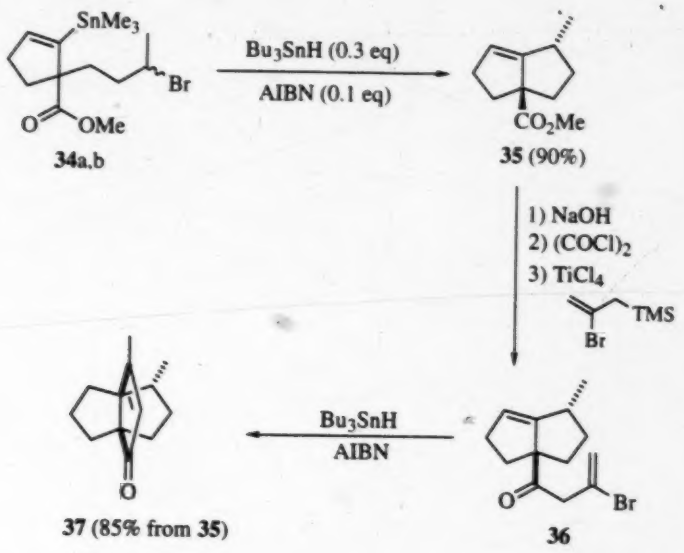


Scheme 8

In work by Mundy (Scheme 8),[11] double alkylation of **29** produced **30a,b** in modest yield. This approach is similar to the strategy of Kraus in the sense that diquinanes **30a,b** contain substituents at both ring junctions. Dehydration followed by hydrogenation then generated di-ester **31**. Methyllithium (2 equiv.) added selectively to one of the carbomethoxy groups of **31** to give heterocyclic propellane **32**, which was later converted by dehydration to the carbocyclic propellane **33**.

Curran used a highly stereoselective radical cyclization (Scheme 9), catalytic in stannane, to generate diquinane **35**,

with a suitable appendage (-CO_2Me) at the ring junction.[12]

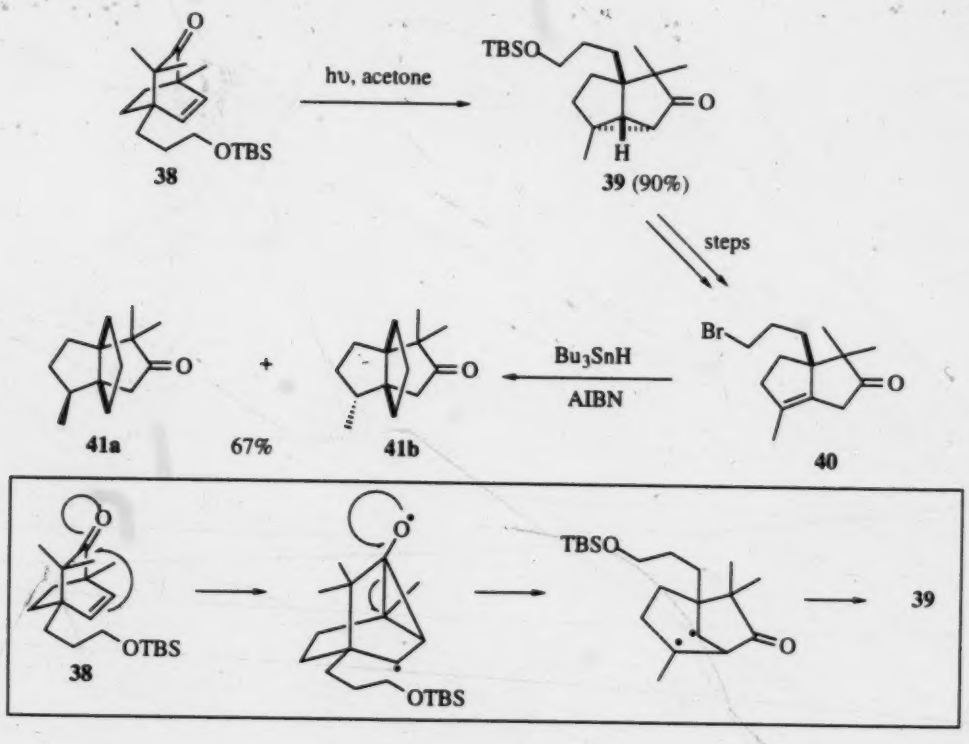


Scheme 9

Elaboration of the methyl ester gave vinyl bromide **36**, which then underwent a standard 5-*exo*-*trig* radical closure to form propellane **37**. This was the first reported case of radical cyclization being used to construct a propellane system. Curran would later improve on the efficiency of this concept, by introducing a tandem radical cyclization process (*vide infra*).

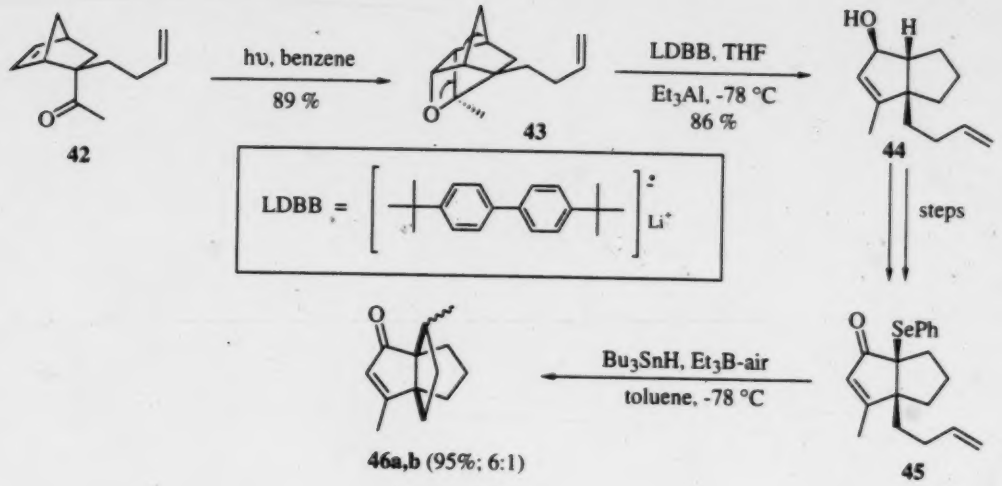
In another unique approach to a diquinane (Scheme 10),[13] irradiation of compound **38** triggered an oxa-di-π-methane rearrangement (see mechanism in Scheme 10) to give diquinane **39**, with an appropriate tether at the ring junction. This compound was further transformed (**39** → **40**) to a suitable radical cyclization precursor. The 5-*exo* closure then

proceeded smoothly to give diastereomeric propellanes **41a,b**. This oxa-di-π-methane rearrangement would later be used by other researchers to form, not simply a diquinane, but a propellane directly (*vide infra*).



Scheme 10

Rawal, in a very recent publication,[14] has also used radical cyclization for the construction of a propellane skeleton (Scheme 11). His construction of the diquinane core is the most notable aspect of the work. Upon irradiation of norbornene derivative **42**, an intramolecular photocycloaddition occurred to give oxetane **43**.



42 43 44 45 46a,b (95%; 6:1)

Scheme 11

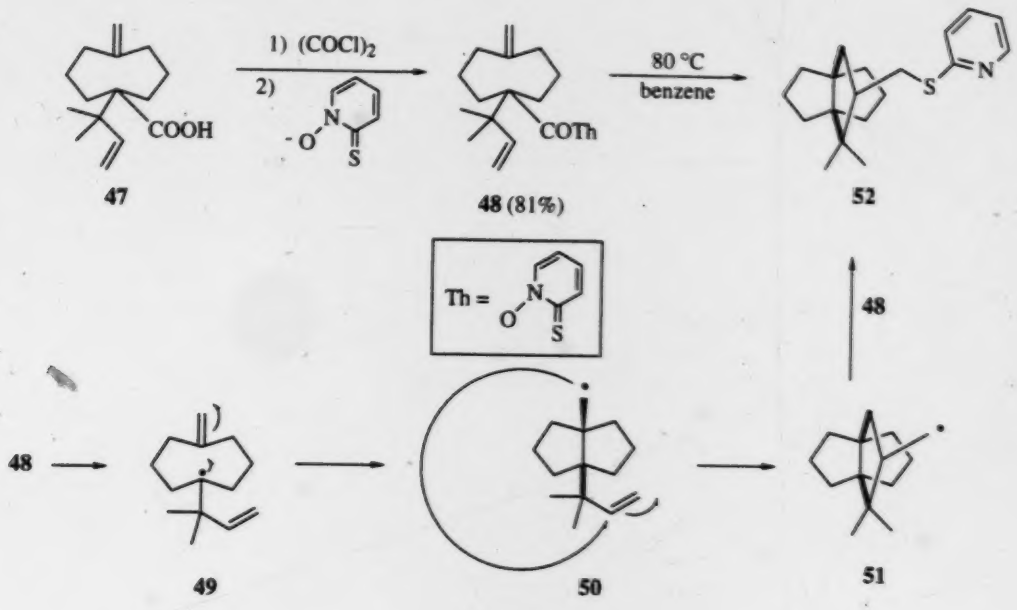
Treatment of **43** with LDBB and Et_3Al promoted cleavage of the oxetane C-O bond and concomitant fragmentation of the back bond of the norbornane skeleton, affording diquinane **44** in high yield. Completion of the propellane synthesis was then straightforward; formation of an α-selenoketone (**44** → **45**, standard reagents) followed by radical cyclization, gave a mixture of propellanes **46a,b**.

3. Tandem processes

Tandem processes offer the opportunity to rapidly construct the propellane skeleton in a single step. Because of the unusual architecture of the target compounds, substrates must be carefully designed in order to achieve propellane formation.

Curran has improved on his earlier stepwise synthesis of a propellane by discovering a tandem transannular radical

cyclization process (Scheme 12)[15] in which all three rings of the system are assembled in a single step.



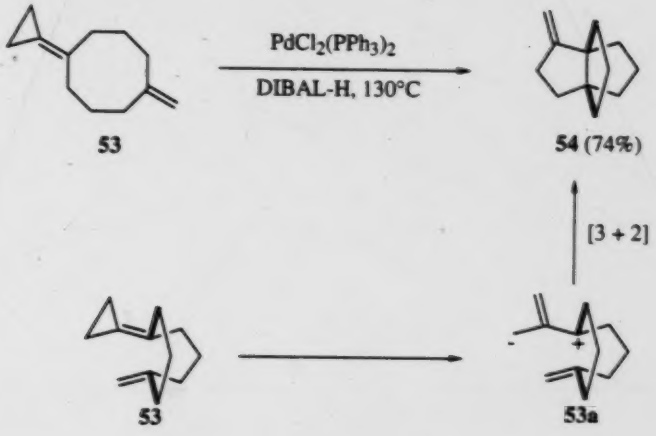
Scheme 12

The carboxylic acid moiety of **47** (itself available in several steps) was converted into a thiohydroxamate ester (Barton radical precursor)[16] and, upon heating, propellane **52** was formed in good yield. The thiopyridyl moiety in **52** is a suitable handle for further transformations; for example, Curran converted it into an exocyclic methylene by elimination of the corresponding sulfoxide.

Mechanistically, the tertiary radical **49** (initiated by a thermally-induced decarboxylation of **48**) underwent transannular cyclization onto the exomethylene unit.

Standard 5-*exo* radical closure then gave propellane intermediate **51**, which added to another molecule of **48**. This final step not only produces compound **52** but also acts as the radical chain-propagating reaction.

Another transannular ring closure approach is that of Nakamura, who used palladium catalysis to effect intramolecular cycloaddition between a methylenecyclopropane moiety and an olefin.[17] Scheme 13 shows one example; other propellanes were constructed as well.

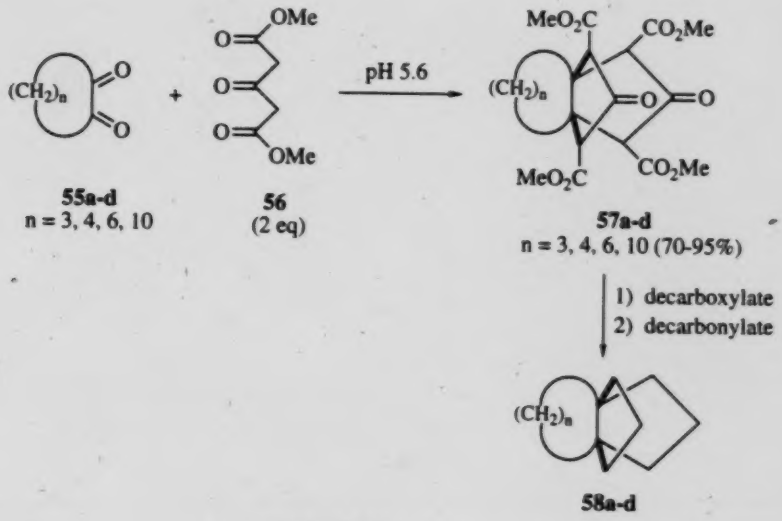


Scheme 13

A simplified mechanism is given in Scheme 13; the reaction proceeds via a trimethylenemethane intermediate.[18] The 1,3-dipole intermediate **53a** can be considered a trimethylenemethane synthon; certainly, a more realistic picture would show the metal coordinated to the methylenecyclopropane moiety. Therefore, **53a** is not a true intermediate in the reaction; it does, however, illustrate

nicely the bond formation that would occur in the next step. The reaction is also highly sensitive to the nature of the substrate, as small changes in the structure of **53** caused the reaction to fail.

With appropriate choices of substrates, Cook has cleverly used the Weiss reaction[19] to construct a series of propellanes (Scheme 14).[20]



55a-d
n = 3, 4, 6, 10

56
(2 eq)

57a-d
n = 3, 4, 6, 10 (70-95%)

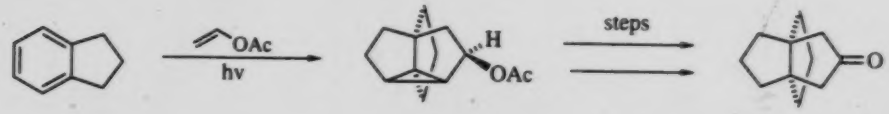
58a-d

Scheme 14

Thus, acid-catalyzed condensation of a series of 1,2-diones (**55a-d**) with dimethyl 3-ketoglutarate **56** gave propellanes **57a-d** in high yields. The main drawback to this method is the presence of excess functionality, which may be undesired. In this case, those functional groups were efficiently removed by decarboxylation and reduction.

Wender's work[21] has closely paralleled the pioneering studies of Srinivasan[22] on arene-olefin *meta* cycloadditions.

Using this strategy, a propellane skeleton was quickly assembled in one step (Scheme 15). Irradiation of indan in the presence of vinyl acetate afforded cyclopropane-containing propellane **59**, albeit in low yield. The mechanism of the reaction is beyond the scope of this review, but the course of the reaction is such that many different regiochemical pathways are possible.



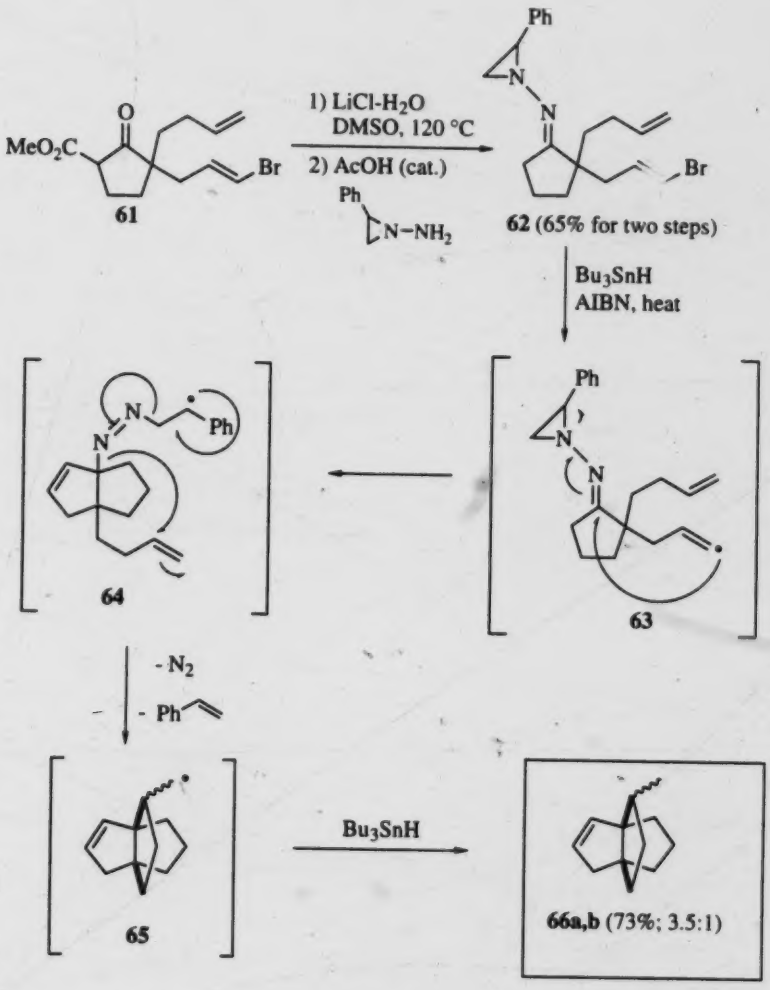
indan — **59** (21%) — **60**

Scheme 15

The possibility of multiple product formation is a key limitation to this procedure, and indeed, accounts for the low yield in this case, as other products were observed as well. Hydrogenolysis of the cyclopropane (along with other steps) gave a more traditional propellane **60**.

The cleverness of Curran's tandem radical cyclization approach (seen earlier) was matched a few years later by Lee's group (Scheme 16).[23] Substituted cyclopentane **61** was converted to *N*-aziridinyl imine **62** via decarboxylation and imine formation. Tandem radical cyclization then gave a mixture of diastereomeric propellanes **66a,b**. The mechanism of the process begins with the addition of a vinyl radical (5-*exo*) to the imine, followed by aziridine cleavage to generate a stable benzylic radical **64**. Expulsion of styrene

and a nitrogen molecule (see **65**) leads to 5-*exo*-*trig* closure to give the [3.3.3]propellane skeleton.

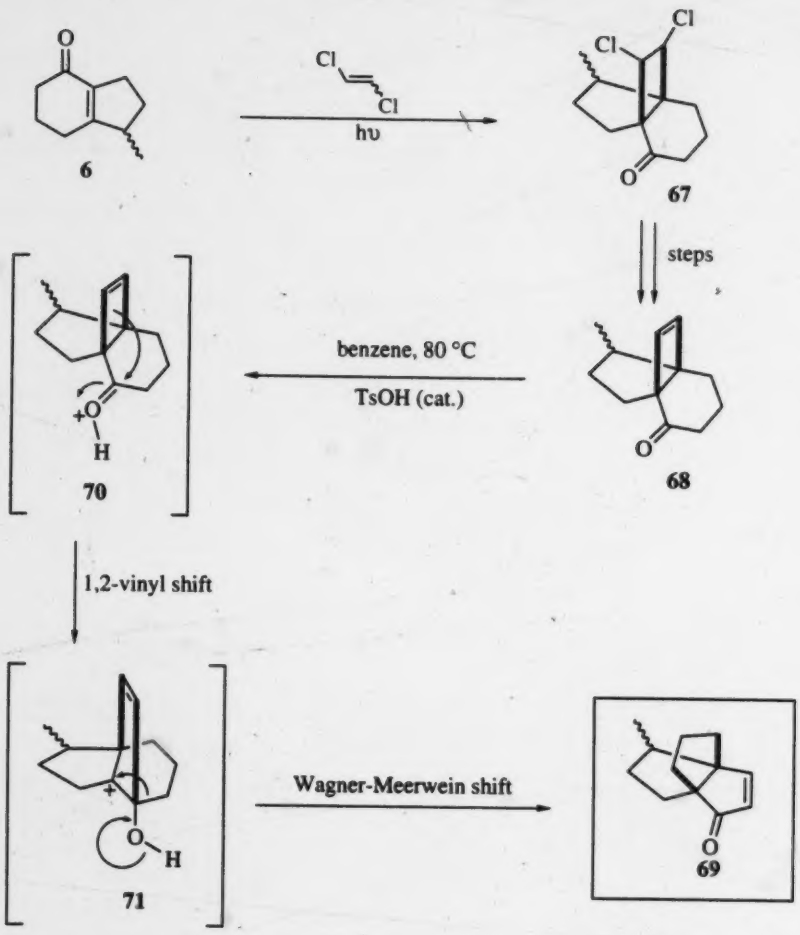


Scheme 16

4. Propellanes via Rearrangements

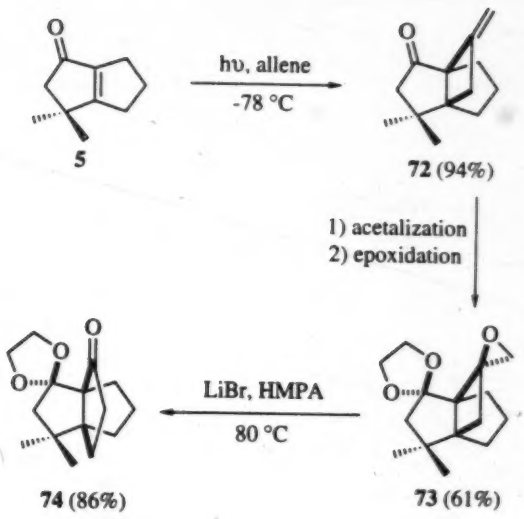
Rearrangements, like the tandem processes just covered, offer a more elegant, if not more efficient, way of constructing propellane systems. The examples which fall into this category all have in common a rearrangement, or a series of rearrangements, as the key step in the construction of the propellanes. In this section, we see again the use of some bicyclic enones of the type which were introduced in Figure I-4.

In Smith's synthesis of a [3.3.3]propellane (Scheme 17),[24] enone **6** was efficiently converted into the [4.3.2]propellane **68** via a 2+2 cycloaddition and reductive elimination. Upon heating in the presence of an acid catalyst, rearrangement takes place to afford the [3.3.3]propellane **69**. The mechanism of this transformation is given in the Scheme. Initial activation of the carbonyl unit by TsOH induces a 1,2-vinyl shift (**70** → **71**) to form a stable tertiary carbocation, and Wagner-Meerwein shift completes the rearrangement, to give propellane **69**. Many similar propellanes have been made by Cargill[25] using these cyclobutenyl moieties as rearrangement precursors, and indeed, Smith's work closely resembles these earlier studies.



Scheme 17

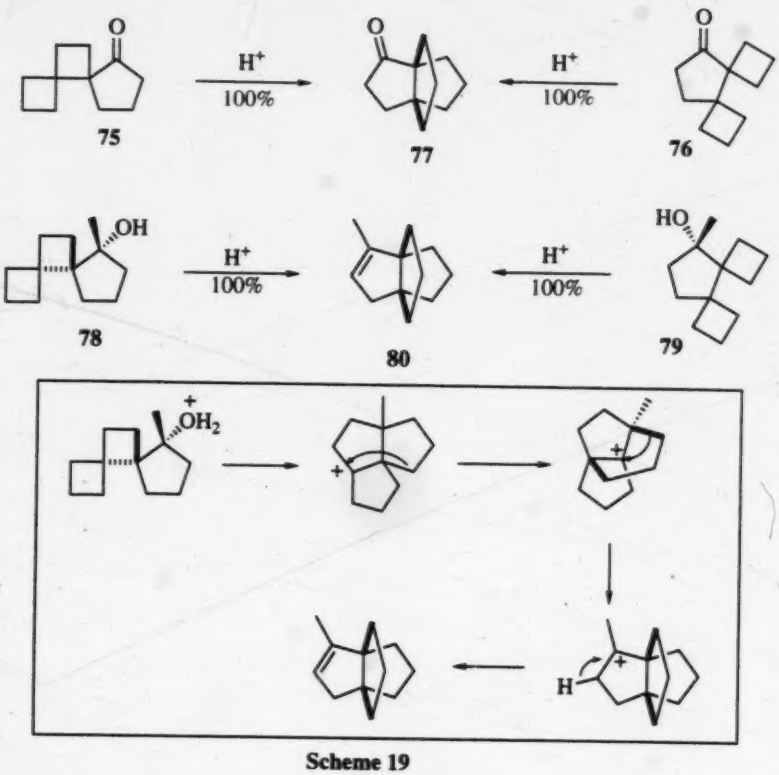
A regioselective ring enlargement was the key step in Tobe's synthesis of a propellane (Scheme 18).[26] Irradiation of enone **5** in the presence of allene gave the "head-to-head" isomer **72** as the major product. Ketalization and epoxidation then provided access to the key intermediate **73**. Bromide opening of the epoxide, followed by regioselective ring enlargement, afforded propellane **74** as the major product.



Scheme 18

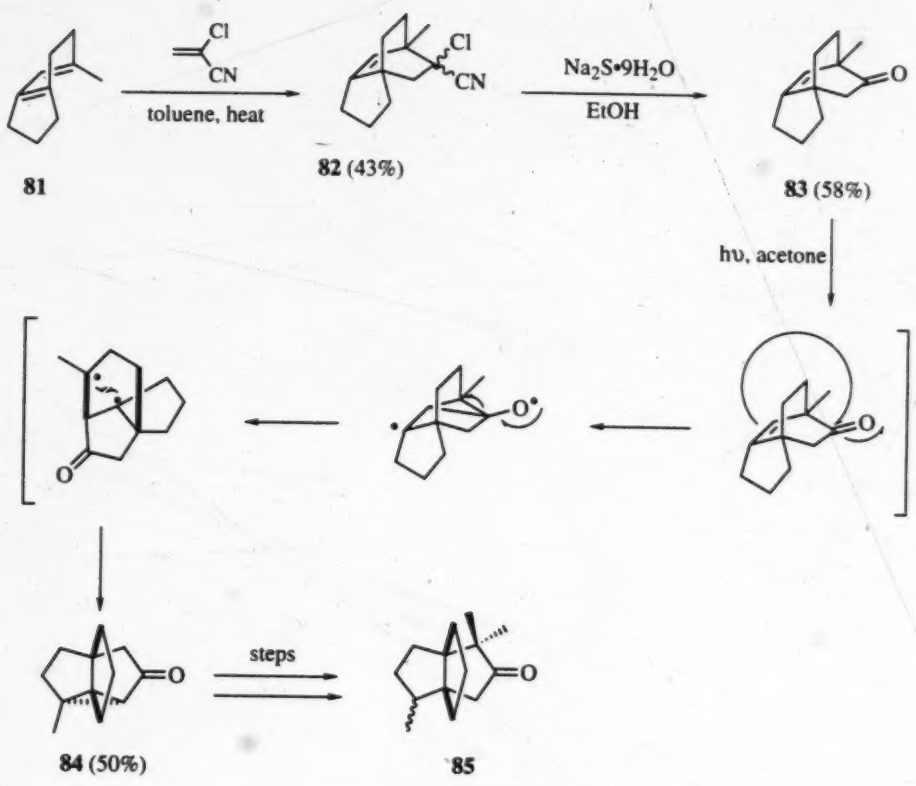
Majewski has achieved remarkable yields of [3.3.3]propellanes (Scheme 19)[27] by exploiting the acid-catalyzed rearrangements of dispiro[3.0.4.2]undecanes and dispiro[3.0.3.3]undecanes. These conversions take place by a series of alkyl shifts; a specific mechanism for the conversion **78** → **80** is shown in Scheme 19. Acid-catalyzed rearrangements of similar cyclobutyl-containing compounds have also been used by other groups to make propellanes.[28]

In part 1 of this literature survey, an oxa-di-π-methane rearrangement was described in the construction of a diquinane core for further elaboration into a propellane (Scheme 10).



Scheme 19

A similar strategy has been employed by Mehta,[29] and, with some modifications of the substrate, he has synthesized a propellane directly by this process (Scheme 20). Diels-Alder reaction of α-chloroacrylonitrile with bicyclic diene **81** gave **82** as the major product, albeit in modest yield. Further modification afforded the desired norbornene derivative **83**. Upon irradiation of **83**, an oxa-di-π-methane rearrangement[30] takes place (see mechanism in Scheme 20) to give propellane **84** directly in reasonable yield. The cyclopropyl moiety in **84** (which is generally undesired in these processes) was easily removed to give propellane **85**.



81

82 (43%)

83 (58%)

84 (50%)

85

Scheme 20

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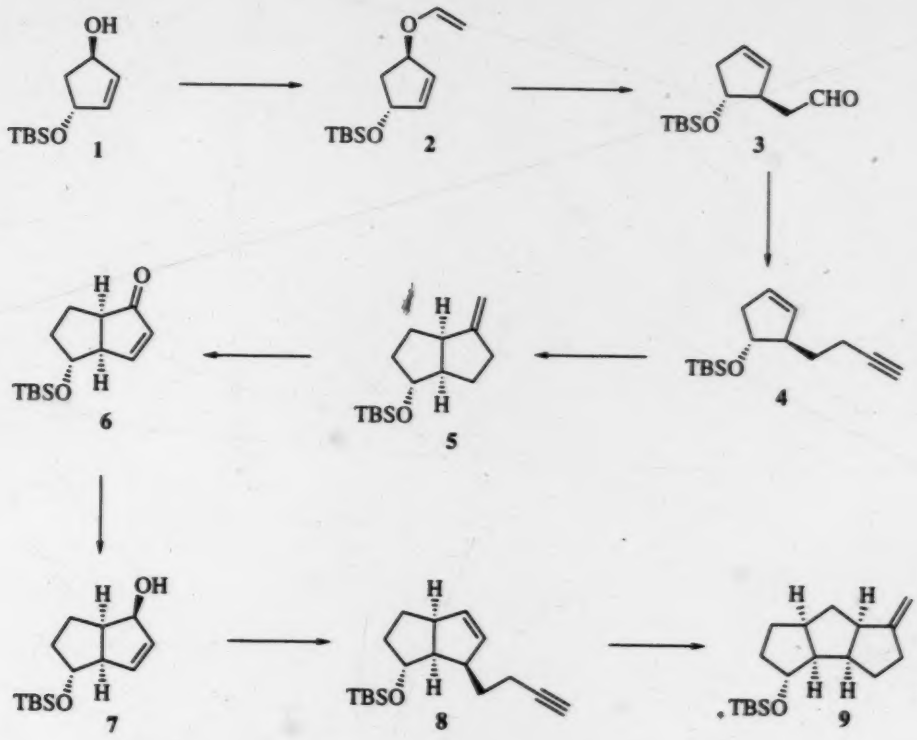
RESULTS AND DISCUSSION

1. Introduction

At the outset of this work, there was ample precedent for the synthesis of propellanes by radical cyclization, as can be seen in the preceding literature review. Radical cyclization has proved to be a very effective method of forming crowded quaternary carbon centers, as are found in propellanes.

Our design of a suitable substrate paralleled some earlier work completed in our laboratory by Manning. This work[1] described an iterative route to triquinanes by radical cyclization; the general strategy used is shown in Scheme 1. The starting material for this sequence was allylic alcohol **1** and the initial step was the conversion of the hydroxyl group into a vinyl ether. Claisen rearrangement of the 1,5-diene gave a cyclopentane ring with a tether that was then modified. Elaboration of the aldehyde into a chain extended acetylene afforded an enyne system, which is a suitable substrate for radical cyclization. The key radical cyclization step involved addition of a tributyltin radical to the terminal end of the acetylene. In this process, a vinyl radical is created, which then cyclizes in a 5-*exo* fashion onto the endocyclic double bond, creating diquinane **5**, which can be converted by standard chemistry into an α,β-unsaturated enone (**6**).



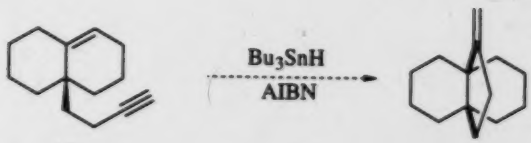
Scheme 1 - Iterative Route to Triquinanes

When this enone is reduced (in a 1,2-fashion), allylic alcohol **7** is obtained, which is a compound of the same class as the original starting material. Therefore, the entire process can be repeated to generate an additional ring. The final result is the formation of a triquinane (**9**).

2.1 [4.4.3]Propellanes by Enyne Cyclization

Our goal was to extend this methodology by studying whether enyne radical closure could be used to construct propellanes. The plan is similar to that shown in Scheme 1 - a simple adjustment to the radical cyclization precursor is

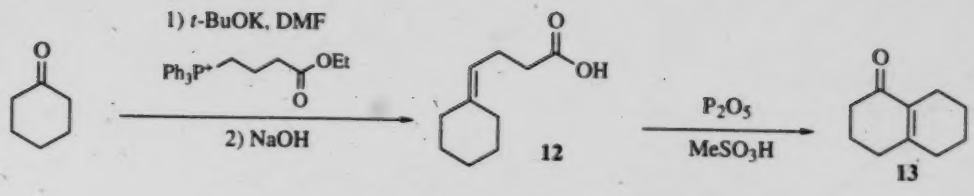
needed. Thus, if enyne **10** were to cyclize (as the previous enyne had done), one would obtain a [4.4.3]propellane (Scheme 2). The prospects for success were good, as our proposed cyclization was to occur on a similar substrate to that used by Manning. One potential difficulty we envisioned, however, was the presence of a doubly substituted sp^2 carbon at C(5) (compare **4** and **10**). This situation has been observed to retard the rate of 5-*exo* cyclization in other substrates[2] (Table I-1). In order to test the effectiveness of the radical cyclization, the synthesis of enyne **10** became our immediate goal.



10 **11**

Scheme 2 - Proposed Synthesis of Propellanes

The starting material chosen for this study was bicyclic enone **13**. It was available in multigram quantities via a known three-step procedure.[3] The literature procedure was modified slightly (Scheme 3), the modification coming in the final step, conversion of **12** into bicyclic ketone **13**. Rather than using polyphosphoric acid (PPA) for this transformation, as in the reported route, we used Eaton's reagent,[4] which is a commercially available mixture of phosphoric and methanesulfonic acids.

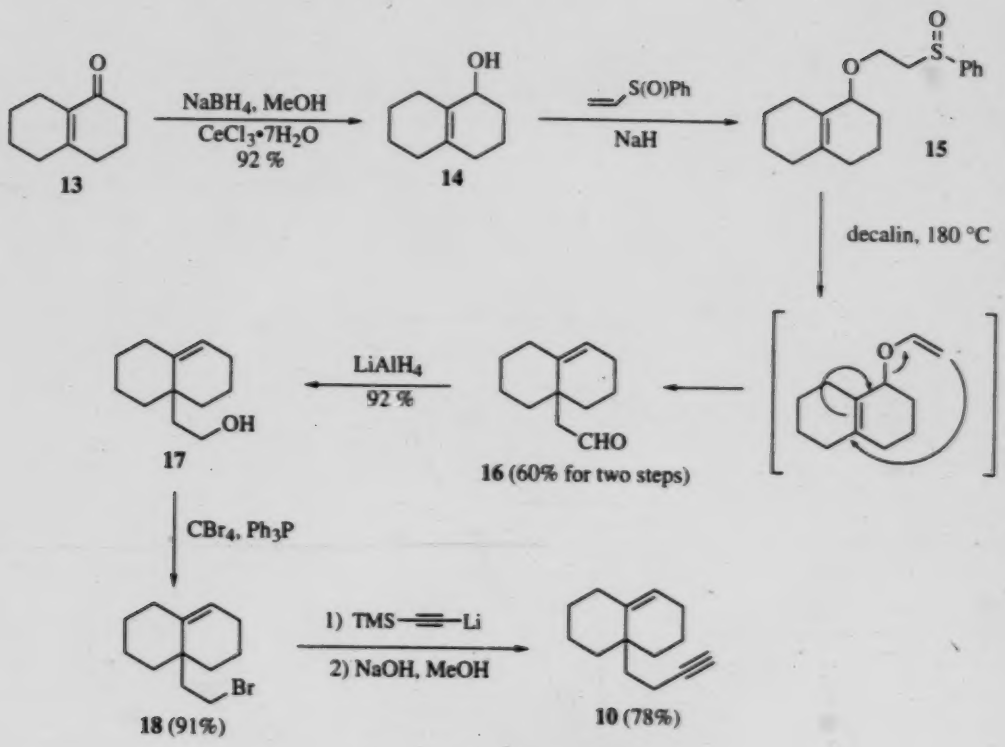


Scheme 3 - Preparation of Starting Material

The use of Eaton's reagent has two considerable advantages: a) it is an easily handled liquid while PPA is an extremely viscous syrup (magnetic stirring is only possible at *ca.* 70 °C, at which point it becomes less viscous), and b) the temperature at which the transformation occurs is lower in the case of Eaton's reagent (about 60 °C versus 110 °C). With multigram quantities of **13** in hand, we began the sequence of reactions that would lead to the radical cyclization precursor **10**.

Luche reduction[5] of enone **13** proceeded as expected, to give allylic alcohol **14**. Deprotonation of the alcohol (NaH), followed by Michael addition to phenyl vinyl sulfoxide,[6] gave compound **15**, which could not be completely purified due to co-elution with phenyl vinyl sulfoxide. The crude material was used directly in the next step: at high temperature, *in situ* formation of a vinyl ether occurs, followed by Claisen rearrangement, to provide aldehyde **16**. The alternative sequence for the Claisen rearrangement (mercury-catalyzed formation of the vinyl ether,[7] followed by TRIBAL-induced Claisen rearrangement[8]) was attempted and was successful at times; however, formation of the vinyl ether could not be

reproduced consistently.

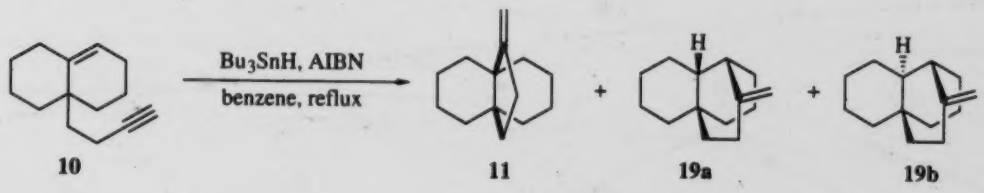


Scheme 4 - Synthesis of the Enyne

Therefore, we used the more reliable process indicated in Scheme 4. Formation of the enyne was then completed by standard reactions: reduction (CHO → CH_2OH), replacement of the hydroxyl by bromine, and finally, reaction with an acetylide. The cyclization could now be tested with enyne **10**.

Treatment of enyne **10** with tributyltin hydride in benzene (reflux) using AIBN as the radical initiator gave a mixture of three compounds, whose structures we took to be

11, **19a**, and **19b** (Scheme 5). The compounds were inseparable by chromatography. Conversion of the exocyclic methylene moieties to carbonyls by ozonolysis also gave three inseparable (by flash chromatography) compounds. The presence of three compounds precluded rigorous characterization of each one.



Scheme 5 - Results of Enyne Radical Cyclization

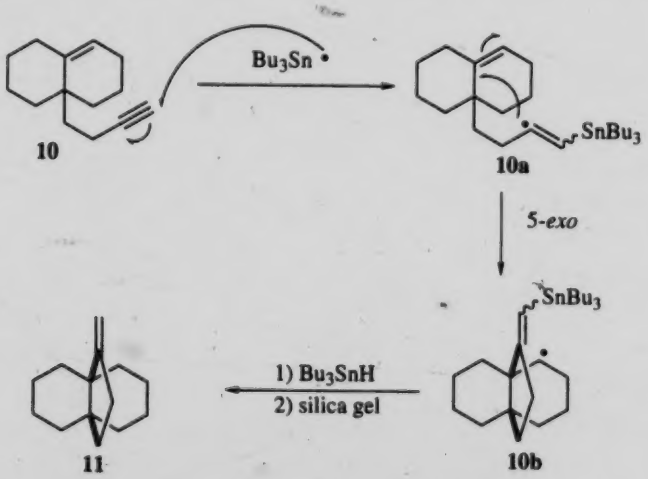
The main evidence which we used to assign the structures came from the ^{13}C NMR APT spectrum. Two features of the spectrum allowed us to assign the structures.

1) The presence of six carbon signals in the alkene region supports our assignment of three compounds, each with an olefin moiety present. Furthermore, the relative shifts of each carbon of the olefin is indicative of a $R_2C{=}CH_2$ type olefin.[9] This conclusion is also supported by the attached proton test.

2) The attached proton test indicates the presence of only four carbon atoms having a single proton. This would correspond to compounds **19a** and **19b**, each of which has a pair of such carbon atoms. The remaining carbons of all three compounds are either quaternary, or have two protons

attached.

The indicated structural assignment is, of course, consistent with a large body of information on radical closures. The mechanism of formation of the three proposed compounds deserves some comment. Formation of the desired propellane occurred by a standard radical cyclization mechanism (Scheme 6). Addition of a tributyltin radical to the terminal end of the acetylene results in a highly reactive vinyl radical. A 5-*exo* radical closure then takes place (**10a** → **10b**), in the process forming a propellane intermediate. Finally, quenching of this radical intermediate with tributyltin hydride, followed by destannylation (silica gel),[10] gave propellane **11**.

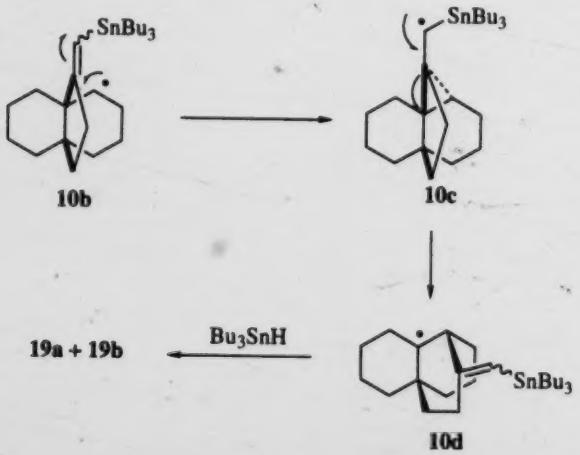


Scheme 6 - Mechanism of Formation of Propellane 11

Formation of the two undesired isomers could have occurred in two ways, by analogy with literature precedents. Possibly, both are operating, but we were unable to confirm

this.

In the first pathway, radical intermediate **10b** (formed by the 5-*exo* cyclization mentioned previously), rather than being quenched by Bu_3SnH, instead undergoes a cyclopropyl radical rearrangement (**10b** → **10c**). The radical in **10c** then rearranges to a stable tertiary radical (**10d**). Quenching of this radical by tributyltin hydride can take place from either face of the system, and this accounts for the formation of two isomers, **19a** and **19b**. Cyclopropyl radical rearrangements are well-known in systems of this type.[11] One possible driving force for this process is formation of a more stable tertiary radical from a secondary radical (compare **10b** and **10d**).



Scheme 7 - Cyclopropyl-Radical Rearrangement Pathway

The second possible pathway is supported by a study by Beckwith, in which the relative rates of 5-*exo* vs. 6-*endo* cyclizations were analyzed.[2,12] The conclusion of the study

was that, on increasing substitution at C(5), the 6-*endo* cyclization pathway becomes more favored (Table I-1).

For our substrate, C(5) is disubstituted while C(6) is mono-substituted. It is likely then, that the vinyl radical formed by tin radical addition to the acetylene would undergo 6-*endo* radical closure onto the double bond (**10a** → **10d** in Scheme 8).

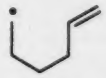
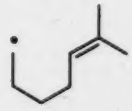
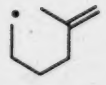
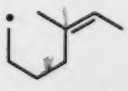
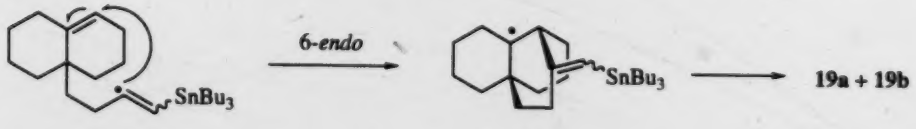
Entry	radical	k_{rel} exo	k_{rel} endo
1		1.0	0.02
2		2.4	<0.01
3		0.022	0.04
4		0.022	<0.002

Table I-1 - Relative Cyclization Rates for Substituted Hexenyl Radicals

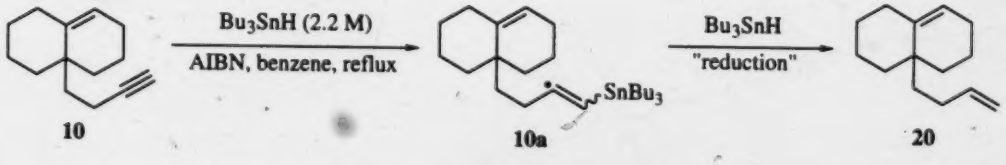
This would result in the same intermediate (**10d**) observed in the cyclopropyl rearrangement pathway; and again, quenching of radical **10d** from either face of the system would account for the production of isomers **19a** and **19b**.



10a **10d**

Scheme 8 - 6-*endo* Pathway

Assuming the cyclopropyl rearrangement was, at least in part, the cause of the undesired compounds, we attempted to suppress the rearrangement by repeating the reaction at a much higher concentration of tin hydride (Scheme 9). This alteration has been applied before by other groups with some success.[11] The rationale behind the change is that intermediate radical **10b**, in the presence of a higher concentration of tin hydride, would be quenched immediately before undergoing the cyclopropyl rearrangement. However, in this experiment, we observed simple reduction of the intermediate vinyl radical **10a**; hence, the concentration of tin hydride was too high.

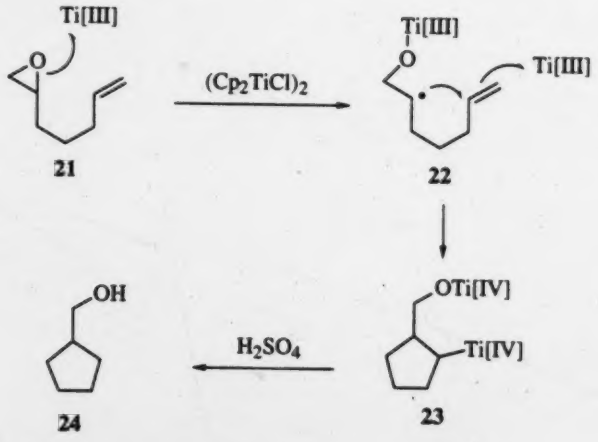


Scheme 9 - Radical Reaction at Higher Tin Hydride Concentration

We did not try intermediate concentrations of tin hydride to test the idea further as, at this point, we had decided that our enyne radical closure was not general for the synthesis of propellanes. Therefore, we adopted a new strategy based on the use of epoxides as radical precursors.

2.2. [4.4.3]Propellanes from Epoxides

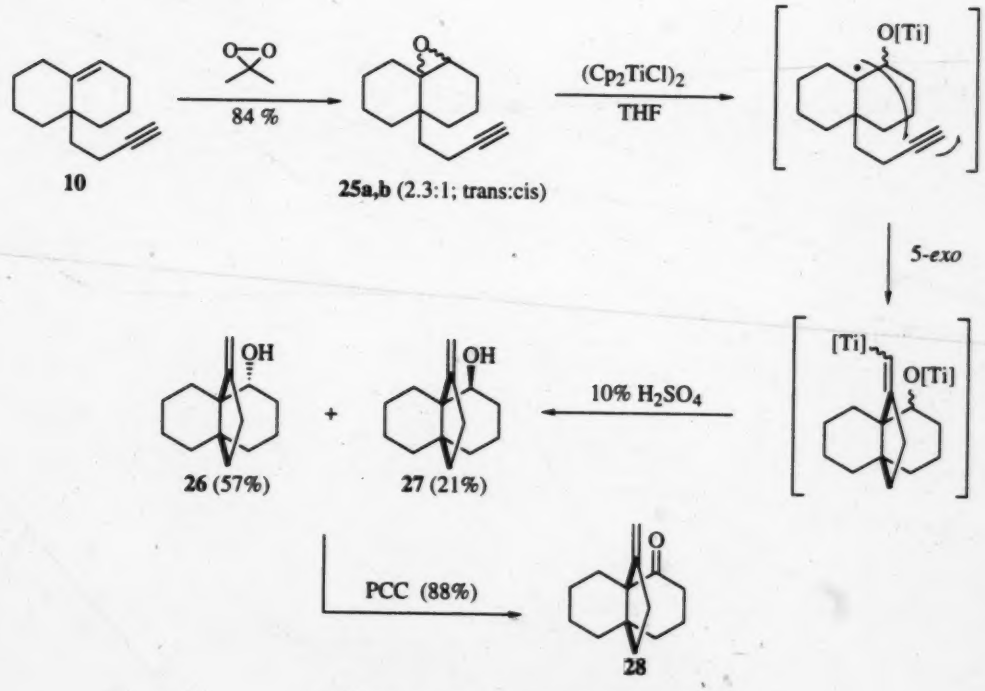
In a study by RajanBabu and Nugent a few years ago, it was established that epoxides could act as radical precursors and that the resulting radicals could undergo cyclization onto suitable radical acceptors.[13] Scheme 10 shows one example in which epoxide cleavage by a titanium(III) species occurs regioselectively (formation of a secondary radical is favored over the formation of a primary radical). The secondary radical then underwent 5-*exo* closure onto the double bond to give ring system **23**. The titanium moiety was then removed by treatment with sulfuric acid. This concept had also been used previously in our group in a synthesis of ceratopicanol.[14]



Scheme 10 - RajanBabu/Nugent Epoxide Cyclization

Scheme 11 illustrates our strategy for taking advantage of the epoxide opening. Enyne **10** (our earlier radical precursor) was further transformed into an inseparable

mixture of diastereomeric epoxides **25a** and **25b** by the use of dimethyldioxirane. The 2.3:1 ratio was known by measuring the relative integration in the ^1H NMR spectrum of the epoxide mixture. At this point, there was no way to tell that the *trans* isomer was the major compound; this assignment came at a later stage.

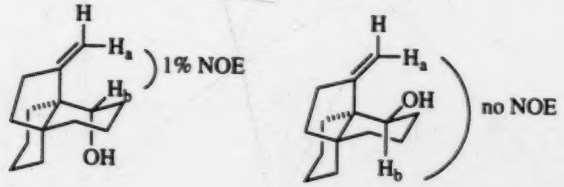


Scheme 11 - Epoxide Route to Propellanes

As expected from the literature precedents, epoxide cleavage occurred regioselectively to give a tertiary radical (as opposed to a secondary radical). 5-*Exo* closure onto the triple bond then gave a di-titanium intermediate. Work-up of the reaction mixture with aqueous sulfuric acid afforded propellane alcohols **26** and **27**, easily separable by

chromatography. The relative amounts of each isomer obtained is simply a consequence of the initial ratio of the diastereomeric epoxides. Oxidation (PCC) of the alcohols then produced a single compound (**28**) in 88% yield.

The assignment of stereochemistry for the propellane alcohols was done by examining NOE enhancements. Figure I-5 shows 3-D structures of each isomer. On examination of these models, it appeared possible that isomer **26** may show an NOE correlation between protons H_a and H_b. This enhancement would not be possible in isomer **27** due to the large distance between the protons. For isomer **27**, as expected, irradiation of proton H_a caused no NOE enhancement of proton H_b. For isomer **26**, irradiation of H_a resulted in a 1% enhancement of H_b. Although the enhancement is small, our ability to examine both isomers makes the structure assignment reliable.



26 **27**

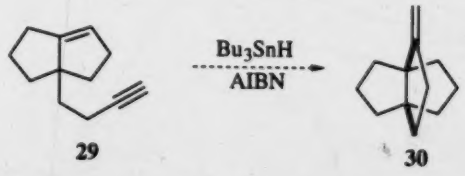
Figure I-5 - Assignment of Alcohol Stereochemistry by NOE Measurements

The structure assignment in Figure I-5 is also supported by other spectral information. On the assumption of a chair conformation for the six-membered rings, compound **26** would be expected to have the hydroxyl-bearing carbon at lower field[15] in the ^{13}C NMR spectrum than **27**. The ^{13}C NMR spectrum shows

that these expectations are met and, on this basis, the stereochemistry is tentatively assigned.

2.3 [3.3.3]Propellanes by Enyne Cyclization

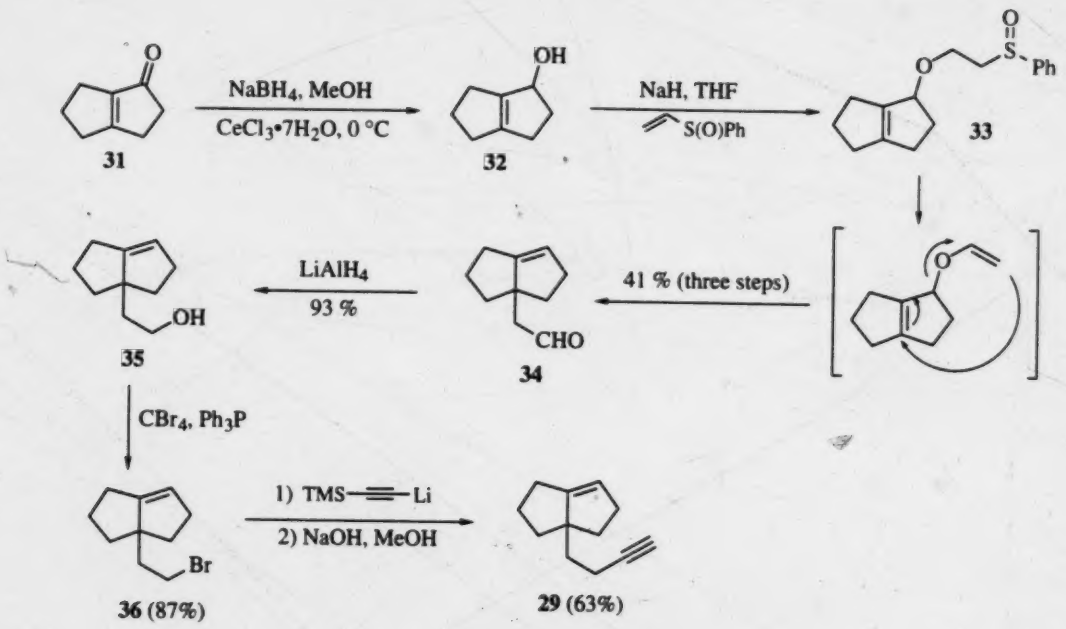
With a synthesis of [4.4.3]propellanes by radical closure available, we turned our attention to formation of the [3.3.3]propellane system, a more interesting system in terms of natural product synthesis.[16] Our strategy was identical to the previous case, and the initial target was enyne **29**. Despite the failure of the enyne radical cyclization to efficiently form propellanes previously, we still wanted to test that concept on this new compound.



29 **30**

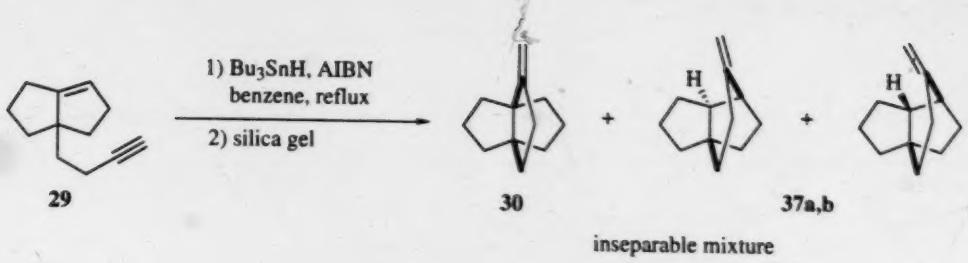
Scheme 12 - Proposed Synthesis of [3.3.3]Propellanes

Our starting material for this study was bicyclic enone **31**. We obtained multigram quantities of this compound via a two-step literature procedure.[17] The route from enone **31** to our required enyne **29** followed a pathway (Scheme 13) virtually identical to that in our earlier study. The experimental procedures and observed yields were very similar, and so, a discussion of the pathway is not warranted here.



Scheme 13 - Route to the Enyne

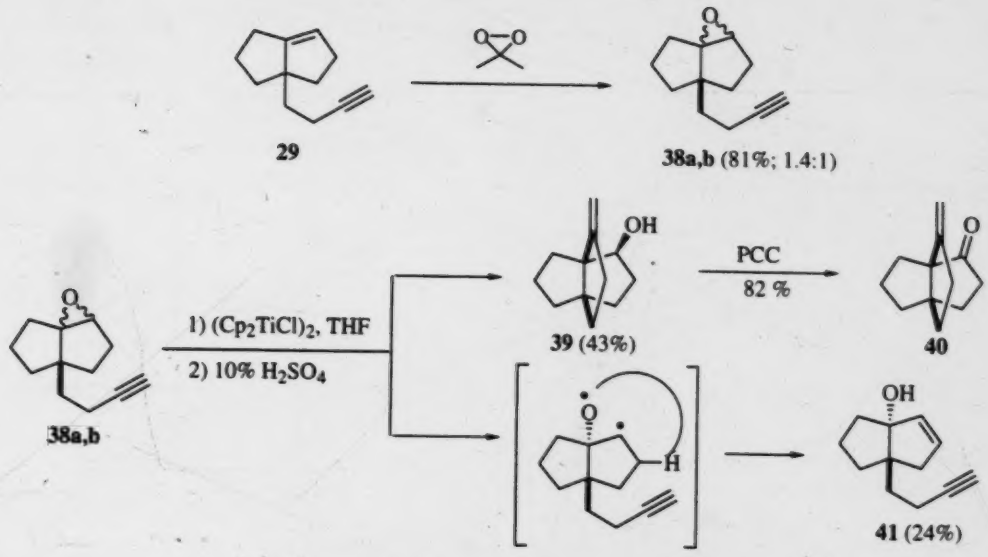
The results of the tin-mediated radical cyclization of enyne **29** (Scheme 14) closely paralleled our earlier study; an inseparable mixture of three isomers was obtained. The mechanism of formation of these compounds would be the same as in our previous case. Again, we could not fully characterize the compounds, and as in the earlier series, structure assignment was done by considering ^{13}C evidence (*vide supra*).



Scheme 14 - Results of the Enyne Cyclization

2.4 [3.3.3]Propellanes from Epoxides

The next logical step was to test the effectiveness of the RajanBabu strategy to form propellanes from **29**. Epoxidation of enyne **29** proceeded smoothly (dimethyldioxirane) to give an inseparable mixture of epoxides (Scheme 15). The 1.4:1 ratio was determined from the ^{1}H NMR spectrum, although we could not determine which isomer was the major product of the epoxidation. Radical cyclization of epoxides **38a** and **38b** was then carried out under the same conditions as used previously (Ti-induced epoxide cleavage). Upon examination of the reaction mixture by TLC, it appeared that two isomeric propellanes had been formed (two distinct new spots were formed on the TLC plate). When the spectra for these two compounds were measured, however, it was clear that our initial speculation was not correct.



Scheme 15 - Results of the Epoxide-Radical Cyclization

Reaction of one of the epoxide isomers had indeed resulted in formation of a propellane (**39** in Scheme 15) by the standard 5-*exo* radical closure pathway. However, the other isomer underwent a different reaction pathway to give **41**. It should be noted here that we did not determine which of the epoxides underwent which pathway. Thus, the assigned stereochemistries of **39** and **41** are tentative. The high strain energy of the *trans*-fused ring system of one of the epoxide substrates may be a factor in the differing reaction pathways.

2.5 Conclusions

In this study, we determined that propellane formation via enyne radical cyclization is not a general process. While both [4.4.3] and [3.3.3]propellanes could be made, the

formation of side products made this an inefficient process. Changing the acetylene to the radical acceptor rather than the radical source (by using the RajanBabu epoxide route) was found to be a more promising method, especially in the synthesis of [4.4.3]propellanes. However, the efficiency of this approach is sensitive to the structure of the substrates, as we observed in our attempts to construct [3.3.3]propellanes.

The efficiency of propellane formation via enyne radical cyclization might possibly be improved by the presence of an electron-withdrawing group (such as a cyanide, ester, or sulfone) at the less-substituted carbon of the alkene. This modification would promote a 5-*exo* pathway at the expense of the 6-*endo* pathway, but it is unclear whether the cyclopropyl rearrangement pathway would be suppressed, and the synthesis of substrates bearing such electron-withdrawing groups would undoubtedly be quite involved.

The presence of a gem-dimethyl group in the acetylenic pendant of our enyne substrates might also serve to promote 5-*exo* closure, as such an effect has been observed previously.[12] Furthermore, this modification may allow rapid construction of the modhephene (Figure I-2) skeleton.

Experimental

Argon was purified by passage through a column (3.5 x 42 cm) of BASF R-311 catalyst and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography or extractions were distilled. Petroleum ether refers to the fraction bp 35-60 °C.

Products were isolated from solution by evaporation under water pump vacuum at, or below, 30 °C, using a rotary evaporator.

The term "inseparable mixtures" refers to a mixture of compounds which could not be separated by flash chromatography. No further separation techniques were attempted.

Purity of compounds is based on NMR (^{1}H and ^{13}C) spectra.

Flash chromatography silica gel was used for filtrations of crude product mixtures.

Temperatures recorded for Kugelrohr distillations refer to air-bath temperatures and are not true boiling points. The values indicate the temperature at which the distillate begins to condense in the receiving bulb.

Melting points were determined on a Kofler block melting point apparatus.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by examination under UV light or by spraying the plate with a solution of phosphomolybdic acid, followed by charring on a hot plate. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry THF was distilled from Na and benzophenone ketyl. Dry PhH was distilled from Na. Dry *i*-Pr_2NH, CH_2Cl_2, MeOH, pyridine, DMF, and HMPA were distilled from CaH_2, the last two solvents being distilled under water pump vacuum. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

Infrared spectra were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent and using potassium bromide plates.

Proton nuclear magnetic resonance spectra were recorded with Bruker WP-200 (at 200 MHz), or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent with Me_4Si as an internal standard. ^{13}C NMR spectra were recorded with Bruker WP-200 (at 50.3 MHz), Bruker AM-300 (at 75.5 MHz), or Bruker AM-400 (at 100.6 MHz) spectrometers, using $CDCl_3$ as an internal standard. The symbols s', d', t', and q' used for ^{13}C NMR spectra indicate 0, 1, 2, or 3 attached protons.

Mass spectra were recorded with an AEI Model MS-12 or MS-50 mass spectrometer at an ionizing voltage of 70V.

Microanalyses were performed by the microanalytical laboratory of this Department.

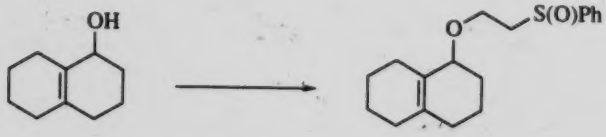
(±)-1,2,3,4,5,6,7,8-Octahydro-1-naphthalenol (14).

13 **14**

$CeCl_3 \cdot 7H_2O$ (4.656 g, 12.50 mmol) was added to a stirred and cooled (0 °C) solution of enone **13**[3] (1.562 g, 10.4 mmol) in MeOH (100 mL). $NaBH_4$ (0.985 g, 26.0 mmol) was added via a side-arm addition tube over 15 min and, after 2 h, water (100 mL) was added to the resulting slurry. (Acid must be avoided in the work-up in order to prevent formation of a very non-polar UV-active compound.) The clear aqueous solution was extracted with EtOAc until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:9 EtOAc-hexane, gave alcohol **14** (1.454 g, 92%) as a pure (^1H NMR, 200 MHz), colorless solid: mp 51-53 °C; FTIR ($CHCl_3$ cast) 3319 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.20-2.05 (m, 14 H), 2.15-2.45 (m, 1 H), 3.90 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 18.2 (t'), 22.8 (t'), 23.0 (t'), 27.0 (t'), 30.3 (t'), 30.6 (t'), 32.2 (t'), 68.7 (d'),

129.9 (s'), 132.7 (s'); exact mass *m/z* calcd for $C_{10}H_{16}O$ 152.1201, found 152.1200. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 79.01; H, 10.29.

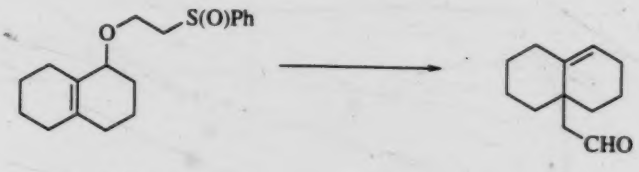
[2-(1,2,3,4,5,6,7,8-Octahydronaphthalen-1-yloxy)ethyl] phenyl sulfoxide (15).



14 **15**

Alcohol **14** (1.670 g, 10.99 mmol) in dry THF (15 mL) was added dropwise at room temperature to a stirred suspension of NaH (80% suspension in mineral oil, 330 mg, 11.0 mmol) in dry THF (50 mL). After 30 min, a solution of phenyl vinyl sulfoxide (5.02 g, 33.0 mmol) in dry THF (10 mL) was added dropwise. A trace (*ca.* 1 mg) of KH (35%$^{w}/_{w}$ in mineral oil) was then added as a catalyst. After 1 h, EtOAc (50 mL) and water (50 mL) were added. The aqueous phase was extracted with EtOAc until extraction was complete (TLC control, silica, 1:1 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:1 EtOAc-hexane, gave a mixture of sulfoxide **15** and phenyl vinyl sulfoxide, inseparable by chromatography. The mixture was used directly in the next step.

(±)-1,3,4,5,6,7-Hexahydro-4a(2*H*)-naphthaleneacetaldehyde (16).

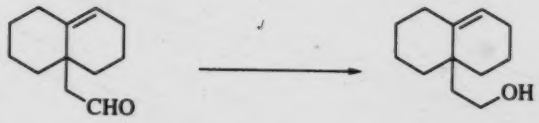


15 **16**

$NaHCO_3$ (35.63 g, 424 mmol) was added in one lot to a stirred solution of sulfoxide **15** (prepared from 1.670 g of **14**, contaminated with phenyl vinyl sulfoxide) in dry, purified decalin (50 mL). The suspension was heated at 180 °C for 5 days, and then cooled to room temperature. EtOAc (100 mL) and water (50 mL) were added, and the organic phase was washed with brine, dried ($MgSO_4$), and evaporated. Decalin was removed by flash chromatography, using hexane, and the desired compound was then eluted with EtOAc. Evaporation of the EtOAc eluant, and flash chromatography of the residue over silica gel (3 x 18 cm), using 15:85 CH_2Cl_2-hexane, gave aldehyde **16** (1.182 g, 60% over two steps) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (neat) 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10-2.35 (m, 14 H), 2.45 (dd, J = 14.0, 3.0 Hz, 1 H), 2.68 (dd, J = 14.0, 3.0 Hz, 1 H), 5.40-5.60 (m, 1 H), 9.83 (dd, J = 4.0, 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 18.7 (t'), 21.9 (t'), 25.3 (t'), 28.0 (t'), 32.2 (t'), 36.9 (t'), 37.6 (s'), 39.2 (t'), 48.3 (t'), 121.8 (d'), 140.8 (s'), 203.6 (d'); exact mass *m/z* calcd for $C_{12}H_{18}O$ 178.1358, found 178.1361. Anal. Calcd for $C_{12}H_{18}O$:

C, 80.85; H, 10.18. Found: C, 80.54; H, 10.14.

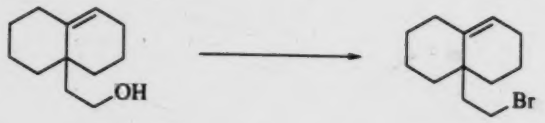
(±)-1,3,4,5,6,7-Hexahydro-4a(2*H*)-naphthaleneethanol (17).



16 **17**

Aldehyde **16** (1.00 g, 5.62 mmol) in THF (10 mL) was added to a stirred and cooled (-78 °C) suspension of $LiAlH_4$ (107 mg, 2.81 mmol) in dry THF (30 mL). The mixture was allowed to warm to room temperature, and then cooled to 0 °C. Water (10 mL) was added and the aqueous solution was extracted with EtOAc until extraction was complete (TLC control, silica, 1:4 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 1:4 EtOAc-hexane, gave alcohol **17** (933 mg, 92%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR ($CHCl_3$ cast) 3316 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05-1.35 (m, 3 H), 1.40 (s, 1 H), 1.45-1.82 (m, 8 H), 1.82-2.05 (m, 4 H), 2.05-2.40 (m, 1 H), 3.67 (dd, J = 8.4, 7.6 Hz, 2 H), 5.30-5.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.3 (t'), 22.1 (t'), 25.6 (t'), 28.4 (t'), 32.6 (t'), 36.1 (t'), 36.8 (s'), 37.6 (t'), 39.1 (t'), 59.5 (t'), 120.7 (d'), 143.3 (s'); exact mass *m/z* calcd for $C_{12}H_{20}O$ 180.1514, found 180.1517.

(±)-4a-(2-Bromoethyl)-1,2,3,4,4a,5,6,7-octahydro naphthalene (18).



17 **18**

CBr_4 (1.398 g, 4.22 mmol) and Ph_3P (1.106 g, 4.22 mmol) were added successively to a stirred and cooled (0 °C) solution of alcohol **17** (744 mg, 4.13 mmol) in dry CH_2Cl_2 (20 mL). The cold bath was removed and stirring was continued for 2.5 h. The clear solution was then filtered through a short pad (4 x 3 cm) of silica gel, using hexane to wash the residue completely out of the silica. The organic solution was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using hexane, gave bromide **18** (928 mg, 92%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 2926, 2854, 1456, 1445, 1215, 807, 630 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05-1.40 (m, 3 H), 1.40-1.85 (m, 7 H), 1.85-2.35 (m, 6 H), 3.15-3.50 (m, 2 H), 5.30-5.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.2 (t'), 22.0 (t'), 25.4 (t'), 28.2 (t'), 28.9 (t'), 32.3 (t'), 35.4 (t'), 38.3 (t'), 38.9 (t'), 39.0 (s'), 121.3 (d'), 141.7 (s'); exact mass *m/z* calcd for $C_{12}H_{19}{}^{79}Br$ 242.0671, found 242.0670. Anal. Calcd for $C_{12}H_{19}Br$: C, 59.27; H, 7.88. Found: C, 59.17; H, 8.09.

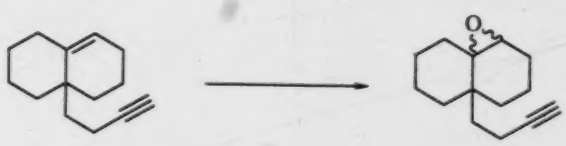
(±)-4a-(3-Butynyl)-1,2,3,4,4a,5,6,7-octahydro naphthalene (10).

18 **10**

n-BuLi (1.6 M in hexanes, 5.15 mL, 8.23 mmol) was added over 5 min to a stirred and cooled (-78 °C) solution of trimethylsilyl acetylene (2.021 g, 20.58 mmol) in dry THF (20 mL). After 15 min, bromide **18** (500 mg, 2.06 mmol) in dry THF (5 mL) was added dropwise. HMPA (2 mL) was added, the cold bath was removed, and stirring was continued for 8 h. MeONa (2.0 M in MeOH, 20 mL, 40 mmol) was then added with stirring and, after 2 h, the mixture was poured into 1:1 hexane-water (50 mL). The aqueous layer was extracted with hexane until extraction was complete (TLC control, silica, hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 22 cm), using hexane, gave acetylene **10** (302 mg, 78%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR ($CHCl_3$ cast) 3310, 2118 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00-1.40 (m, 3 H), 1.40-2.30 (m, 16 H), 5.30-5.50 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.1 (t'), 19.2 (t'), 22.0 (t'), 25.7 (t'), 28.3 (t'), 32.5 (t'), 33.9 (t'), 35.1 (t'), 37.5 (s'), 37.9 (t'), 67.7 (d'), 85.4 (s'), 121.0 (d'), 142.7 (s'); exact mass *m/z* calcd for $C_{14}H_{20}$ 188.1565, found 188.1565. Anal. Calcd for $C_{14}H_{20}$: C, 89.29; H, 10.71.

Found: C, 89.41; H, 10.99.

(±)-4a-(3-Butynyl)octahydro-3*H*-naphth[1,8a-b]oxirene (25a,b).

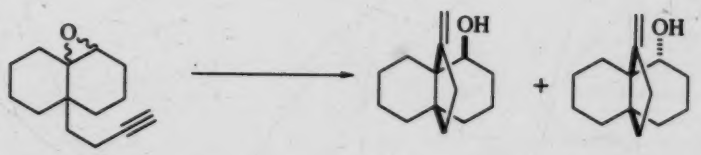


10 **25a,b**

Dimethyldioxirane (0.1 M in acetone, 4.88 mL, 0.488 mmol) was added to a stirred and cooled (0 °C) solution of olefinic acetylene **10** (91.7 mg, 0.488 mmol) in bench acetone (15 mL). The cold bath was removed and, after 2 h, additional dimethyldioxirane was added at room temperature as needed (TLC control, silica, 1:19 EtOAc-hexane) in order to complete the reaction. Water (10 mL) was added and the mixture was extracted with EtOAc until extraction was complete (TLC control, silica, 1:19 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 17 cm), using 1:19 EtOAc-hexane, gave a 2.3:1 mixture (^1H NMR) of diastereomeric epoxides **25a,b** (84.0 mg, 84%) as colorless solids: FTIR ($CHCl_3$ cast) 3307 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85-2.40 (m, 38 H), 2.75-3.00 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) (two signals overlap with two other signals) δ 12.5 (t'), 12.6 (t'), 15.1 (t'), 16.0 (t'), 21.0 (t'), 22.0 (t'), 23.5 (t'), 24.0 (t'), 25.8 (t'), 27.8 (t'), 29.4 (t'), 29.8 (t'), 30.4 (t'), 31.8 (t'), 32.4

(t'), 32.8 (t'), 34.4 (t'), 35.9 (t'), 59.7 (d'), 60.0 (d'), 63.8 (s'), 65.2 (s'), 67.7 (d'), 68.1 (d'), 84.9 (s'), 85.4 (s'); exact mass *m/z* calcd for $C_{14}H_{20}O$ 204.1514, found 204.1497. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.07; H, 9.92.

(1*R,2*S**,6*S**)- and (1*R**,2*R**,6*S**)-(±)-11-Methylenetricyclo [4.4.3.0^{1,6}]tridecan-2-ol (26) and (27).**

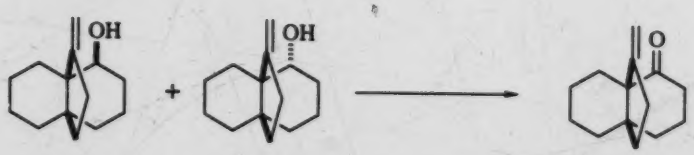


25a,b **27** **26**

$(Cp_2TiCl)_2$ (628 mg, 1.49 mmol) in THF (30 mL) was added to a solution of epoxides **25a,b** (238 mg, 2:1 mixture of diastereomers, 1.17 mmol) in dry THF (20 mL). After 14 h, aqueous H_2SO_4 (50 mL, 10%$^{v}/_{v}$) was added and the aqueous mixture was extracted with EtOAc until extraction was complete (TLC control, silica, 5% EtOAc-hexane). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 16 cm), using 5% EtOAc-hexane, gave alcohol **26** (114 mg, 48%) and alcohol **27** (67 mg, 28%) as pure (^{1}H NMR, 200 MHz), colorless oils. Alcohol **27** had: FTIR (CH_2Cl_2 cast) 3464 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95-2.20 (m, 17

H), 2.25-2.70 (m, 2 H), 3.45 (br s, 1 H), 4.95 (t, J = 3.0 Hz, 1 H), 5.06 (t, J = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 17.1 (t'), 21.6 (t'), 22.2 (t'), 29.1 (t'), 29.3 (t'), 30.2 (t'), 30.7 (t'), 33.1 (t'), 35.3 (t'), 43.5 (s'), 51.6 (s'), 75.1 (d'), 106.3 (t'), 157.7 (s'); exact mass *m/z* calcd for $C_{14}H_{22}O$ 206.1671, found 206.1670. Alcohol **26** had: FTIR (CH_2Cl_2 cast) 3463 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.70-2.45 (m, 17 H), 2.45-2.65 (m, 2 H), 3.38 (dd, J = 14.0, 4.4 Hz, 1 H), 4.83 (t, J = 2.0 Hz, 1 H), 5.03 (t, J = 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.9 (t'), 20.3 (t'), 21.6 (t'), 21.8 (t'), 27.4 (t'), 27.6 (t'), 28.1 (t'), 31.3 (t'), 36.0 (t'), 42.6 (s'), 53.3 (s'), 70.7 (d'), 105.9 (t'), 156.0 (s'); exact mass *m/z* calcd for $C_{14}H_{22}O$ 206.1671, found 206.1670.

(1*R,6*S**)-(±)-11-Methylenetricyclo[4.4.3.0^{1,6}]tridecan-2-one (28).**

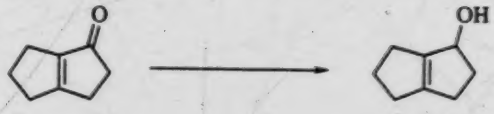


27 **26** **28**

A mixture of diastereomeric alcohols **26** and **27** (53.0 mg, 0.257 mmol) in dry CH_2Cl_2 (8 mL) was added at room temperature to a stirred mixture of PCC (277 mg, 1.29 mmol) and molecular sieves (4Å, 92 mg) in dry CH_2Cl_2 (10 mL). After 2.5 h, the brown mixture was filtered through a pad (2 x 3 cm) of silica gel, CH_2Cl_2 being used to wash the product completely out of the silica. Evaporation of the filtrate and flash

chromatography of the residue over silica gel (1.5 x 17 cm), using 1:19 EtOAc-hexane, gave ketone **28** (46.0 mg, 88%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR ($CHCl_3$ cast) 1702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90-1.65 (m, 9 H), 1.65-2.30 (m, 6 H), 2.35-2.80 (m, 3 H), 4.52 (t, J = 4.0 Hz, 1 H), 4.80 (t, J = 4.0 Hz, 1 H); ^{13}C NMR (50.3 MHz) δ 21.5 (t'), 21.8 (t'), 23.2 (t'), 28.4 (t'), 30.1 (t'), 30.9 (t'), 32.7 (t'), 34.0 (t'), 38.3 (t'), 49.8 (s'), 63.5 (s'), 106.7 (t'), 156.9 (s'), 212.3 (s'); exact mass m/z calcd for $C_{14}H_{20}O$ 204.1514, found 204.1507.

(±)-1,2,3,4,5,6-Hexahydro-1-pentalenol (32).



31 **32**

$CeCl_3 \cdot 7H_2O$ (6.11 g, 16.4 mmol) was added to a stirred and cooled (0 °C) solution of enone **31** (1.82 g, 14.9 mmol) in bench MeOH (100 mL). $NaBH_4$ (1.41 g, 37.3 mmol) was added via a side-arm addition tube over 15 min. (Care must be taken to keep the reaction mixture at 0 °C. When the reaction mixture was allowed to warm to room temperature, thin-layer chromatography revealed a dark UV-active non-polar spot, presumably the diene formed by dehydration of **32**.) After 1.5 h, water (75 mL) was added to the mixture. The aqueous solution was extracted with EtOAc until extraction was complete (TLC control, silica, 1:4 EtOAc-hexane). The

combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 15:85 EtOAc-hexane, afforded alcohol **32**,[18] which was not characterized due to its instability.

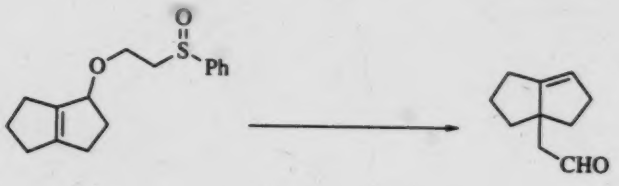
(±)-[2-(1,2,3,4,5,6-Hexahydropentalen-1-yloxy)ethyl] phenyl sulfoxide (33).

32 **33**

Alcohol **32** (1.48 g, 11.9 mmol) in dry THF (30 mL) was added dropwise at room temperature to a stirred suspension of NaH (430 mg, 80% suspension in mineral oil, 14.3 mmol) in dry THF (40 mL). After 30 min, a solution of phenyl vinyl sulfoxide (5.44 g, 35.7 mmol) in dry THF (35 mL) was added dropwise. A trace (*ca.* 1 mg) of KH (35%$^{w}/_{w}$ in mineral oil) was then added as a catalyst. After 0.75 h, EtOAc (30 mL) and water (30 mL) were added. The aqueous phase was extracted with EtOAc until extraction was complete (TLC control, silica, 1:1 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 1:1 EtOAc-hexane, afforded a yellow oil consisting of sulfoxide **33** and phenyl vinyl sulfoxide,

inseparable by chromatography. The mixture was used directly in the next step.

(±)-2,3,4,5-Tetrahydro-3a(1*H*)-pentaleneacetaldehyde (34).



33 **34**

$NaHCO_3$ (34.8 g, 415 mmol) was added in one lot to a stirred solution of sulfoxide **33** (prepared from 1.48 g of alcohol **32**, contaminated with phenyl vinyl sulfoxide) in dry, purified decalin (60 mL). The mixture was heated at 180 °C for 4 days, and then cooled to room temperature. EtOAc (100 mL) and water (50 mL) were added, and the aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 1:4 CH_2Cl_2-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Decalin was removed by flash chromatography, using hexane; the desired compound was then eluted with EtOAc. Flash chromatography of the resulting crude oil over silica gel (3 x 16 cm), using 1:4 CH_2Cl_2-hexane, gave aldehyde **34** (909 mg, 41% over three steps) as a pure (^1H NMR), colorless oil: FTIR (neat film) 1721 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.28-1.52 (m, 1 H), 1.60-1.90 (m, 2 H), 1.90-2.12 (m, 3 H), 2.12-2.32 (m, 2 H), 2.32-2.46 (m, 2 H), 2.46-2.75 (m, 2

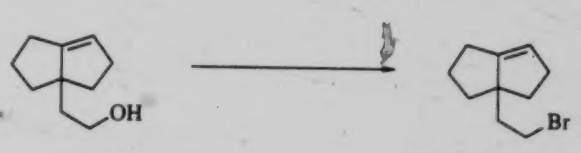
H), 5.20-5.38 (m, 1 H), 9.78 (t, J = 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.5 (t'), 26.0 (t'), 36.0 (t'), 36.8 (t'), 37.3 (t'), 48.8 (t'), 57.1 (s'), 119.0 (d'), 155.1 (s'), 203.2 (d'); exact mass m/z calcd for $C_{10}H_{14}O$ 150.1045, found 150.1033.

(±)-2,3,4,5-Tetrahydro-3a(1*H*)-pentalenoethanol (35).

34 **35**

Aldehyde **34** (730 mg, 4.87 mmol) in THF (10 mL) was added to a stirred and cooled (-78 °C) mixture of $LiAlH_4$ (92.0 mg, 2.43 mmol) in THF (25 mL). The mixture was allowed to warm to room temperature, and was then cooled to 0 °C. Water (15 mL) was added, and the aqueous phase was extracted with EtOAc until extraction was complete (TLC control, silica, 1:4 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 16 cm), using 1:4 EtOAc-hexane, afforded alcohol **35** (688 mg, 93%) as a pure (^1H NMR), colorless oil: FTIR (neat film) 3322 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.15-2.82 (m, 12 H), 3.60-3.85 (m, 3 H), 5.15-5.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.8 (t'), 24.6 (t'), 37.3 (t'), 37.6 (t'), 38.7 (t'), 40.6 (t'), 57.7 (s'), 66.2 (t'), 118.4 (d'), 156.5 (s'); exact mass m/z calcd for $C_{10}H_{16}O$ 152.1201, found 152.1195.

(±)-3a-(2-Bromoethyl)-1,2,3,3a,4,5-hexahydropentalene (36).



35 **36**

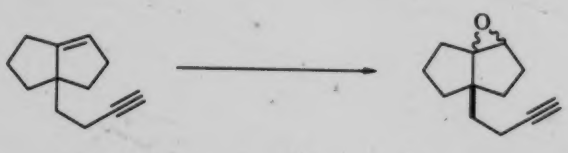
CBr_4 (1.61 g, 4.86 mmol) and Ph_3P (1.28 g, 4.86 mmol) were added successively to a stirred and cooled (0 °C) solution of alcohol **35** (672 mg, 4.42 mmol) in dry CH_2Cl_2 (15 mL). The cold bath was removed and stirring was continued for 2 h. The clear solution was then filtered through a short pad (2 x 1 cm) of silica gel, using hexane to wash the residue completely out of the silica gel. The organic solution was washed with brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue over silica gel (3 x 18 cm), using hexane, gave bromide **36** (827 mg, 87%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (neat film) 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15-2.75 (m, 12 H), 3.28-3.45 (m, 2 H), 5.21-5.27 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6 (t'), 25.9 (t'), 30.2 (t'), 36.6 (t'), 36.7 (t'), 40.0 (t'), 59.8 (s'), 118.6 (d'), 154.9 (s') (We assume a coincident peak); exact mass *m/z* calcd for $C_{10}H_{15}{}^{79}Br$ 214.0358, found 214.0350.

(±)-3a-(3-Butynyl)-1,2,3,3a,4,5-hexahydropentalene (29).

36 **29**

n-BuLi (9.26 mL, 1.6 M in hexanes, 14.8 mmol) was added over 5 min to a stirred and cooled (-78 °C) solution of trimethylsilyl acetylene (3.64 g, 37.0 mmol) in dry THF (30 mL). After 15 min, bromide **36** (796 mg, 3.70 mmol) in dry THF (10 mL) was added dropwise. HMPA (3 mL) was added, the cold bath was removed, and stirring was continued for 6 h. MeONa (35 mL, 2.0 M in MeOH) was then added with stirring and, after 8 h, the mixture was poured into H_2O (75 mL) and hexane (75 mL). The aqueous layer was extracted with hexane until extraction was complete (TLC control, silica, hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using hexane, gave hydrocarbon **29** (375 mg, 63%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (neat film) 3309 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.15-2.80 (m, 15 H), 5.15-5.35 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.7 (t'), 22.6 (t'), 25.8 (t'), 35.0 (t'), 36.4 (t'), 36.5 (t'), 36.5 (t'), 58.9 (s'), 67.7 (d'), 85.5 (s'), 118.2 (d'), 155.4 (s'); exact mass *m/z* calcd for $C_{12}H_{16}$ 160.1252, found 160.1244.

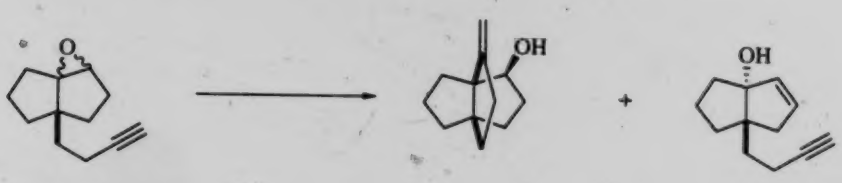
(±)-3a-(3-butynyl)hexahydro-3*H*-pentaleno[1,6a-b]oxirene (38a,b).



29 **38a,b**

Dimethyl dioxirane (18.0 mL, 0.04 M in acetone) was added to a stirred and cooled (0 °C) solution of alkene **29** (192 mg, 1.20 mmol) in bench acetone (20 mL). The cold bath was removed and, after 45 min, water (15 mL) was added. The mixture was extracted with EtOAc until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 21 cm), using 1:19 EtOAc-hexane, provided a mixture of diastereomeric epoxides **38a,b** (170 mg, 81%) as colorless oils: FTIR (CH_2Cl_2 cast) 3294 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.00-2.40 (m, 30 H), 3.24 (t, J = 1.6 Hz, 1 H), 3.69 (t, J = 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.4 (t'), 19.2 (t'), 21.7 (t'), 22.4 (t'), 24.0 (t'), 25.2 (t'), 25.6 (t'), 26.0 (t'), 26.4 (t'), 30.1 (t'), 30.7 (t'), 31.4 (t'), 31.9 (t'), 32.2 (t'), 47.6 (d'), 52.7 (d'), 57.3 (s'), 64.9 (s'), 67.9 (d'), 68.2 (d'), 77.1 (s'), 82.0 (s'), 84.6 (s'), 85.0 (s') (We assume coincident peaks); exact mass *m/z* calcd for $C_{12}H_{16}O$ 176.1201, found 176.1183.

(1*R,2*S**,5*S**)-(±)-8-Methylene-tricyclo[3.3.3.0^{1,5}] undecan-2-ol (39) and (3aα,6aβ)-(±)-6a-(3-Butynyl)-1,3a,4,5,6,6a-hexahydro-3a-pentalenol (41).**

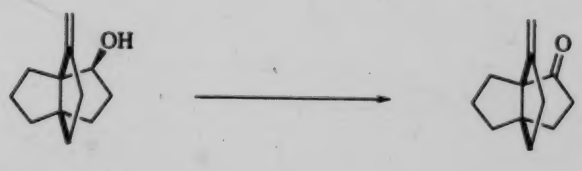


38a,b **39** **41**

$(Cp_2TiCl)_2$ (430 mg, 1.02 mmol) in dry THF (25 mL) was added to a solution of epoxides **38a,b** (142 mg, 0.81 mmol) in dry THF (15 mL). After 12 h, aqueous H_2SO_4 (40 mL, 10%$^{v}/_{v}$) was added and the aqueous mixture was extracted with EtOAc until extraction was complete (TLC control, silica, 1:19 EtOAc-hexane). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 x 16 cm), using 1:19 EtOAc-hexane, afforded alcohol **39** (62.3 mg, 43%) and alcohol **41** (arbitrary stereochemical assignment) (35.2 mg, 24%) as pure (^{1}H NMR, 200 MHz), colorless oils. Alcohol **39** had: FTIR (CH_2Cl_2 cast) 3374 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18-1.95 (m, 13 H), 2.10-2.50 (m, 2 H), 3.70-3.90 (m, 1 H), 4.70-4.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 26.1 (t'), 32.7 (t'), 33.5 (t'), 34.0 (t'), 34.6 (t'), 37.1 (t'), 41.4 (t'), 61.3 (s'), 66.2 (s'), 80.5 (d'), 102.5 (d'), 160.1 (s'); exact mass *m/z* calcd for $C_{12}H_{18}O$ 178.1358, found 178.1357. Alcohol **41** had: FTIR (CH_2Cl_2 cast) 3406, 3306 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ

0.75-2.36 (m, 13 H), 2.45 (dt, J = 17.4, 2.3 Hz, 1H), 5.53 (dt, J = 5.7, 2.2 Hz, 1 H), 5.79 (dt, J = 5.7, 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 15.0 (t'), 22.6 (t'), 36.1 (t'), 39.7 (t'), 39.8 (t'), 45.8 (t'), 51.1 (s'), 68.0 (d'), 85.3 (s'), 94.3 (s'), 132.6 (d'), 135.8 (d'); exact mass *m/z* calcd for $C_{12}H_{16}O$ 176.1201, found 176.1192.

(1*R,5*S**)-(±)-8-Methylenetricyclo[3.3.3.0^{1,5}]undecan-2-one (40).**



39 **40**

A solution of alcohol **39** (40.3 mg, 0.226 mmol) in dry CH_2Cl_2 (10 mL) was added at room temperature to a stirred mixture of PCC (244 mg, 1.13 mmol) and molecular sieves (4Å, 81 mg) in dry CH_2Cl_2 (20 mL). After 30 min, the brown mixture was filtered through a pad (2 x 3 cm) of silica gel, CH_2Cl_2 being used to wash the product completely out of the silica. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.5 x 18), using 1:19 EtOAc-hexane, gave ketone **40** (34.7 mg, 87%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR ($CHCl_3$ cast) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.55 (m, 1 H), 1.55-1.78 (m, 7 H), 1.78-1.90 (m, 1 H), 2.00-2.18 (m, 1 H), 2.18-2.55 (m, 4 H), 4.88 (t, J = 1.3 Hz, 1 H), 4.95 (t, J = 1.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$,

50.3 MHz) δ 27.0 (t'), 31.1 (t'), 34.1 (t'), 37.2 (t'), 37.9 (t'), 38.6 (t'), 40.3 (t'), 59.9 (s'), 69.7 (s'), 106.5 (d'), 154.1 (s'), 219.3 (s'); exact mass *m/z* calcd for $C_{12}H_{16}O$ 176.1201, found 176.1200.

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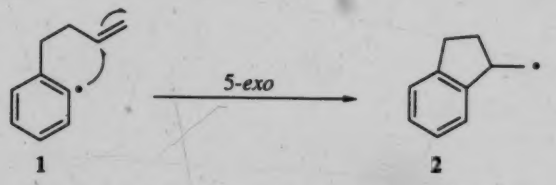
CHAPTER 2 - INTRODUCTION

1. General

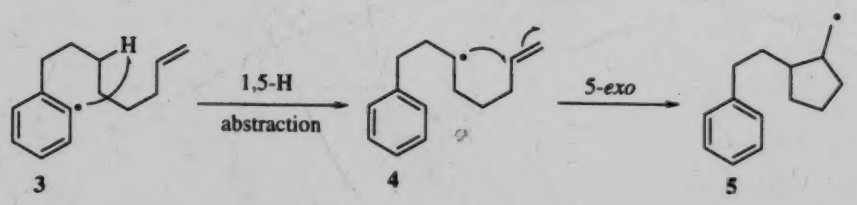
The use of radical reactions in organic synthesis has multiplied greatly in the last fifteen years. Reactions involving radical additions and cyclizations offer certain advantages over ionic processes: the radical reactions usually take place under neutral conditions and thus, avoid the harsh acidic or basic conditions which may be incompatible with other functionalities. In general, radical reactions require only moderate heating, and some of the newer methods of initiation allow one to conduct radical reactions at, or below, room temperature. The general rules for ring closures (Baldwin's rules) also allow a degree of predictability when designing radical cyclizations. Protection and deprotection of certain functional groups (alcohols, ketones, aldehydes) is unnecessary as radicals do not affect these moieties. In addition, radical reactions are rarely complicated by steric factors. With all of these advantages, it is not surprising that the amount of work in this area has increased steadily over the years. The frequency of reviews on the subject[1] is testimony to the rate at which radical chemistry is developing.

Some specific advances in radical chemistry include the development of intramolecular radical cyclization as one of the most effective ways of forming rings, the introduction of new reagents which induce radical formation, and the

development of tandem sequences,[2] which allow multiple ring formation in a single step. One underdeveloped area that has recently garnered increasing interest is that of radical translocation.[3] The concept can be easily understood by comparing a standard radical cyclization reaction (Eq. 1) to a radical translocation process (Eq. 2).



1 2 Eq. 1



3 4 5 Eq. 2

In the translocation procedure, an initial radical (**3**) undergoes a 1,5-hydrogen abstraction to create a radical at a new position (**4**). Cyclization then ensues to give a new compound (**5**). Thus, a radical is generated initially in a favorable location and is translocated to a previously unfavorable position. In the hypothetical example of Equation 2, formation of a radical at the methylene carbon indicated would normally require the prior introduction of a suitable radical precursor. The design of the synthesis must then accommodate this requirement. In effect, radical translocation procedures allow the use of C-H bonds as radical precursors. This is an important development as C-H

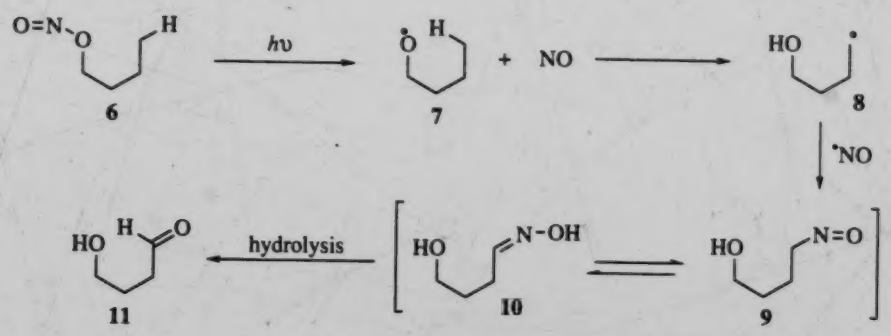
bonds are too strong to be cleaved by the use of tin reagents or other initiators (hence, the need to use other groups as radical precursors).

For the transformation to be successful, the hydrogen transfer should be rapid in order to avoid unwanted side reactions. Therefore, consideration must be given to both the hydrogen donor and the nature of the initial radical. To obtain a kinetically favorable reaction, reactive species such as aryl, vinyl, or alkoxy radicals are often generated in the initial step. Also, since the 1,5 hydrogen transfer occurs at a faster rate than other abstractions (e.g. 1,4 or 1,6), the design of suitable systems almost always involves abstractions of this type. This overview of the literature will focus on some of the useful transformations which have been accomplished using 1,5 hydrogen transfers, as well as some of the problems often encountered in these processes.

2. Historical Perspectives

Although much of the literature involving 1,5-H abstractions has been recent, the process has been in use for a long time. Two early examples demonstrated the potential of the concept. The Barton reaction was introduced as a method to functionalize the remote angular methyl group present in steroids.[4] Scheme 1 illustrates the Barton reaction being used on a simple substrate, the nitrite ester of 1-butanol. Photolysis of the nitrite ester moiety in **6** generates alkoxy radical **7**. Hydrogen abstraction (**7** → **8**)

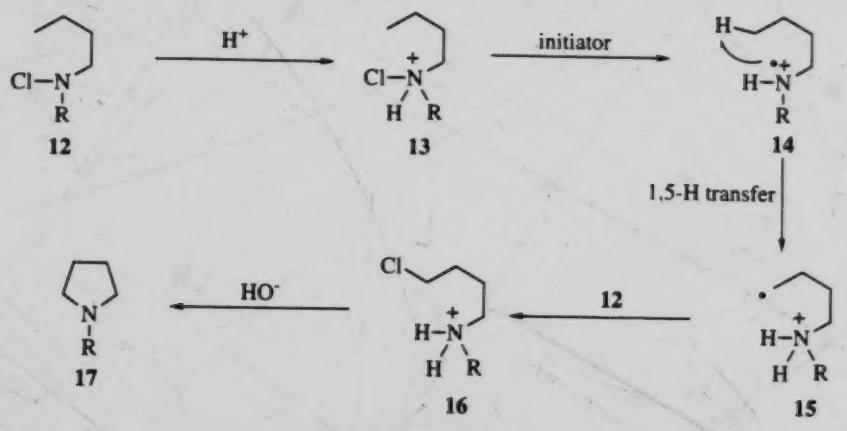
then translocates the radical to the δ position. Nitrosation of the methyl group then ensues, and finally, hydrolysis of the oxime tautomer (**10**) results in formation of an aldehyde. The



Scheme 1 - Barton Reaction

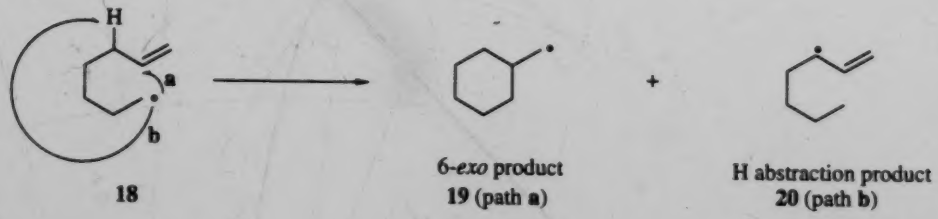
utility of the procedure is seen in this early example, in which a remote unactivated carbon atom can be functionalized.

A related reaction is the Hofmann-Löffler-Freytag reaction (Scheme 2).[5] In this process, the protonated *N*-chloroamine **13** undergoes homolytic cleavage under the influence of heat, light, or initiators, to give protonated aminyl radical **14**. Intermediate **14** then abstracts a hydrogen atom (in a 1,5 fashion) to afford alkyl radical **15**. Chlorine abstraction from **12** gives a chloroalkylammonium ion (**16**), which cyclizes in the presence of base to afford cyclic tertiary amine **17**.



Scheme 2 - Hofmann-Loffler-Freytag Reaction

Despite the success of these early reactions, the 1,5-H abstraction process was rarely used in synthetic planning. For many years, examples of 1,5-H abstractions appeared in the literature as undesired side reactions.[6] A classic example of this involved attempts to perform 6-*exo* radical cyclizations (Scheme 3).



Scheme 3

Radical cyclizations via the 6-*exo* pathway are slower than the more common 5-*exo* pathway. Therefore, the potential exists for side reactions to take place. The 1,5 hydrogen transfer shown in Scheme 3 was often observed in this type of

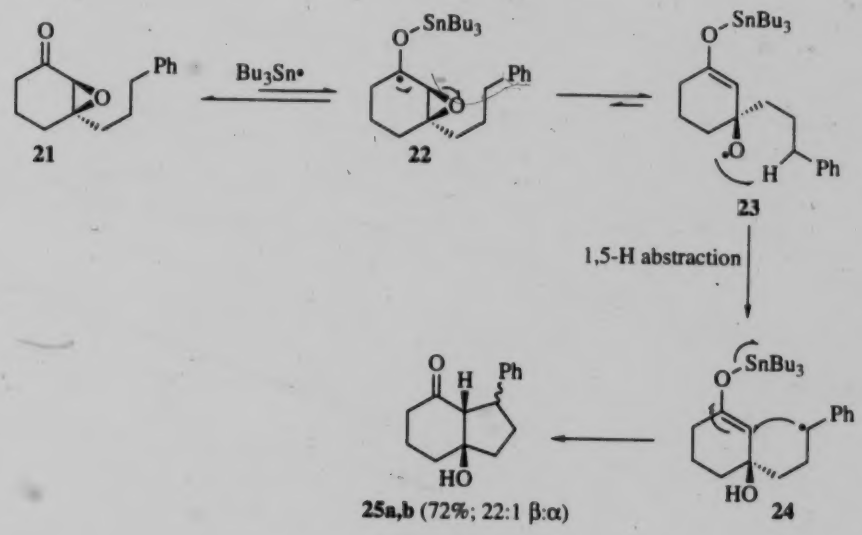
system. The kinetic preference for the 1,5-H abstraction pathway is largely due to the allylic nature of the resulting radical **20**. There were many other examples showing the efficiency of synthetic sequences being compromised by undesired hydrogen abstractions. Despite this, the process has gradually become a valuable tool in organic synthesis.

3. Hydrogen Abstractions by Heteroatom-Centered Radicals

Heteroatom-centered radicals (specifically nitrogen and oxygen) are well-suited to perform hydrogen abstractions, due to their high reactivity. In most cases, the radicals cannot be produced from the parent alcohol or amine, due to the strength of O-H and N-H bonds. Therefore, other methods have been introduced, and some of these methods and their applications will be discussed in the next several examples.

Hydrogen abstractions involving alkoxy radicals can be incorporated into tandem sequences, as shown by Rawal's group. They used a fragmentation-abstraction-cyclization sequence[7] to produce various bicyclic ketones (Scheme 4). Upon exposure to tributyltin radicals, **21** underwent epoxide fragmentation to give alkoxy radical **23**. A 1,5-H abstraction then gave the more stable benzylic radical **24**. Products **25a,b** were then formed by a 5-*exo* ring closure, and expulsion of a tributyltin radical. A number of substrates were tested, and the best yields were obtained in systems where

the 1,5-H transfer leads to a stabilized radical (such as the benzylic radical in Scheme 4). Thus, even a reactive alkoxy radical must be paired with a relatively good hydrogen donor for the abstraction to occur efficiently.



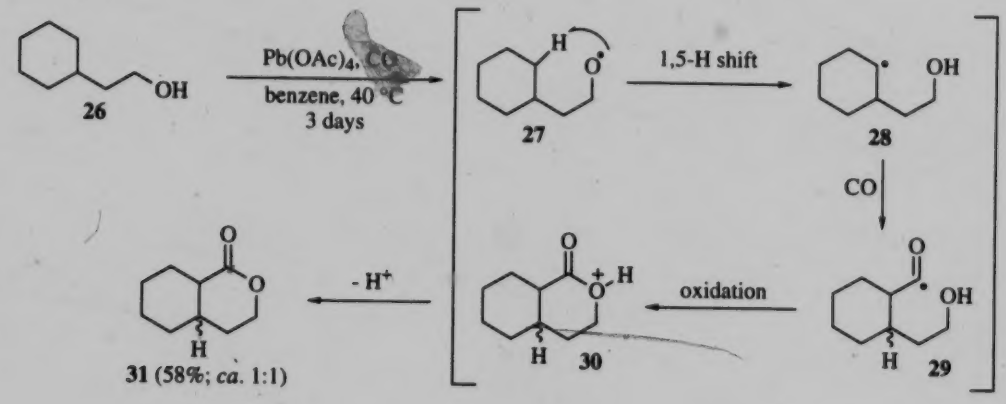
21 22 23 24 **25a,b** (72%; 22:1 β:α)

Scheme 4

The sequence in Scheme 4 could presumably be extended to aziridines although no results have been reported in this area.

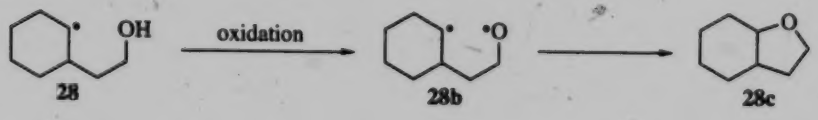
Tsunoi and co-workers have used 1,5-H transfers of alkoxy radicals in the synthesis of a series of δ-lactones (Scheme 5).[8] Treatment of a saturated alcohol, such as **26**, with lead tetraacetate (a one-electron oxidant),[9] generates an alkoxy radical (**27**). Hydrogen abstraction then allows functionalization of the δ carbon (**27** → **28**). Intermolecular trapping of the carbon radical with carbon monoxide then gave acyl radical **29**. The saturated alcohol in **29** is again

oxidized by $Pb(OAc)_4$, and the resulting diradical species (consisting of an alkoxy radical cation and an acyl radical) then couples intramolecularly to give intermediate **30**. Loss of a proton completed the sequence to give **31**, as a pair of diastereomers, in good yield.



Scheme 5

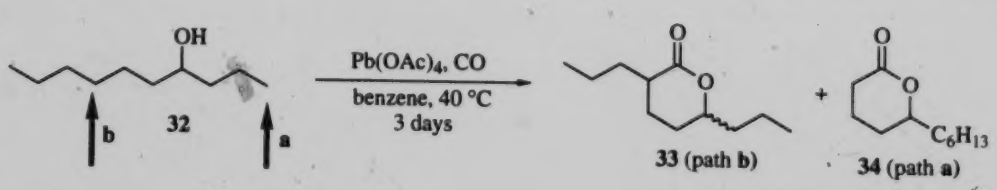
Similar yields were obtained for all of the examples in this study. The main side products that were isolated from the reactions were those produced from the reaction in Equation 3. Thus, the intermolecular trapping of radical **28** with CO must be sufficiently fast to prevent the alternative pathway shown in Equation 3.



Eq. 3

An interesting example in the same study (Scheme 6) nicely illustrates the regioselectivity which can be realized

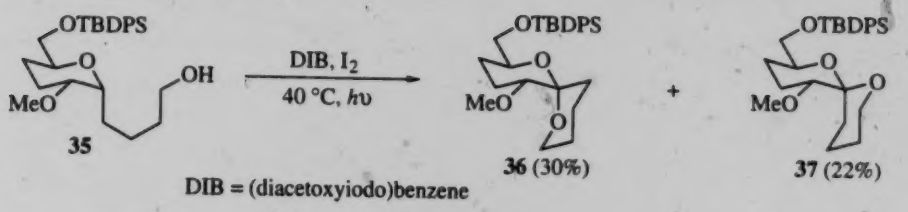
with 1,5-H abstraction processes. In this example, the same mechanism seen previously is in operation. However, the 1,5 hydrogen abstraction can now take place from either of two carbon atoms, position **b** (methylene) or position **a** (methyl). The fact that **33** (from path **b**) is the major product, by far, indicates that CO was incorporated at the methylene carbon with excellent selectivity. This is a consequence of the weaker C-H bond strength of a methylene moiety relative to a methyl group (ΔE = *ca.* 3 kcal/mol).



Scheme 6

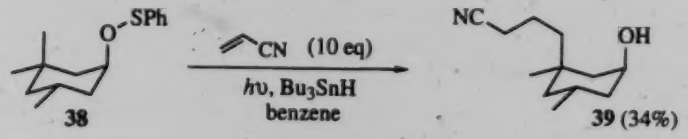
The dispiroacetal system is a basic substructure present in a number of natural polyether antibiotics.[10] These functional groups are often made under acidic conditions,[11] which are incompatible with acid-sensitive functional groups. A milder method for the construction of dispiroacetals involves the use of 1,5-H translocations (Scheme 7).[12] The mechanism of this reaction is virtually identical to the one shown in Scheme 5; [(diacetoxyiodo)benzene, (DIB), like lead tetraacetate, is a one-electron oxidant].[13] The alkoxy radical, in this case, is generated upon irradiation of the galactopyranose derivative **35**. The products obtained were isomeric dispiroacetals **36** and **37**. Isomer **37** can be

converted quantitatively into **36**, if necessary, by treatment with acid.



Scheme 7

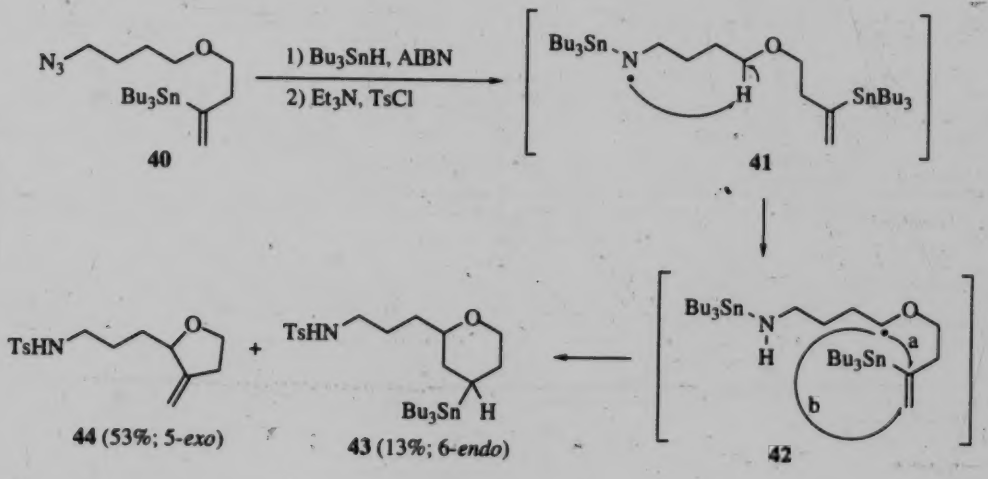
Another method of generating alkoxy radicals is by attaching a phenylsulfide substituent directly onto the oxygen atom, and then cleaving the O-S bond with tin radicals.[14] Product **39** (Scheme 8) was formed upon abstraction of an axial methyl hydrogen by the alkoxy radical, followed by addition to acrylonitrile. This is another variation of the classic Barton reaction and, again, shows the effectiveness of the method for functionalizing sterically encumbered methyl groups.



Scheme 8

Nitrogen-centered radicals, while not as commonly used as their oxygen counterparts, can also cause hydrogen abstractions. One recent development in this area has been described by Kim and co-workers (Scheme 9). Rather than

using standard aminyl radicals, they employed the more nucleophilic *N*-tributyltin substituted aminyl radicals, such as **41**, for radical translocation sequences.[15] The radicals are generated by cleavage of alkyl azides with tributyltin radicals. After 1,5-H transfer (**41** → **42**), cyclization took place by both a 6-*endo* and a 5-*exo* pathway, to produce **43** and **44**, respectively. A similar reaction, using standard aminyl radicals, resulted in less formation of cyclic products, indicating that the 1,5-H transfer in that instance was not as efficient as that in Scheme 9.



Scheme 9

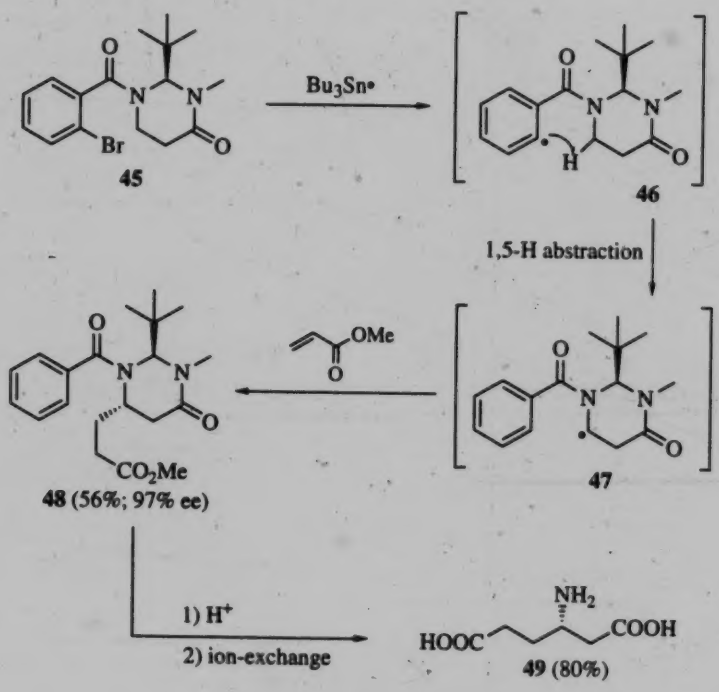
4. Hydrogen Abstractions by Carbon-Centered Radicals

4a. Aryl Radicals

Aryl radicals, like heteroatom-centered radicals, are very reactive, and as such, are appropriate intermediates for hydrogen abstraction sequences. They are almost always

formed by the treatment of aryl halides with tin radicals. The reactivity of aryl radicals is understandable when one considers that aromatic C-H bonds are too strong to be cleaved by radical initiators. This is why aromatic solvents (such as benzene or toluene) are commonly used for radical reactions.

In a fine application of the translocation of aryl radicals, Snieckus and co-workers have made a series of enantiomerically pure β-substituted β-amino acids (Scheme 10).[16] The required substrate for this work was enantiomerically pure **45**.



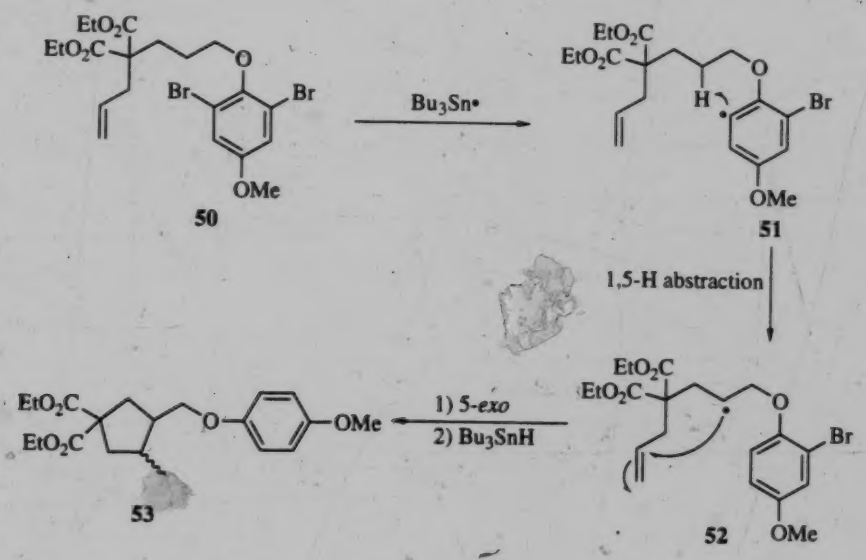
Scheme 10

The aryl radical generated from **45** abstracts a hydrogen

alpha to the amide group, to give intermediate α-amidoyl radical **47**. Intermolecular addition to methyl acrylate then gives **48** in high enantiomeric excess. The stereochemistry at the new chiral center is controlled by the 1,3-asymmetric induction of the *t*-butyl group. Some reduction product (from reduction of radical **47**) was detected as well, indicating that intermolecular H abstraction from Bu_3SnH is a significant competing reaction. This is usually the case in intermolecular radical additions. Compound **48** was easily converted to the β-substituted β-amino acid **49**.

Curran, and others, have introduced the concept of protecting-radical translocating (PRT) groups. A PRT group, as the name suggests, not only acts as a protecting group, but also contains an appropriate radical precursor. Compound **50** in Scheme 11 has such a dual-purpose functional group in the form of an alcohol, protected as a substituted phenyl ether.[17] The initially-produced aryl radical **51** abstracts a hydrogen β to the oxygen atom. Ring closure (5-*exo*) then produces a cyclized compound with the alcohol still suitably protected as a substituted phenyl ether. Some uncyclized material was also recovered, due to reduction of radicals **51** and **52**. The presence of two bromines in the *ortho* positions of the aromatic ring generally results in increased yields of cyclized product. This is due to the fact that, if radical **51** or **52** is reduced prior to undergoing cyclization, a second bromine atom on the aromatic ring will, in effect, give the cyclization a second opportunity to occur. The concept of

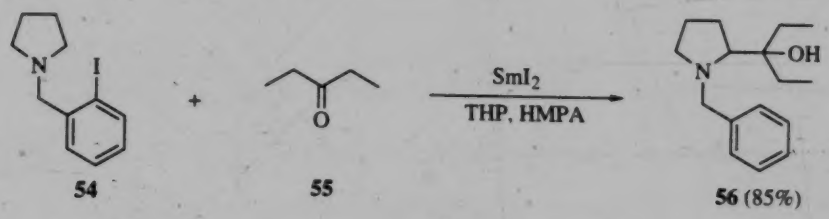
PRT groups is not limited to alcohols; it has also been applied to amides,[18] amines,[19] and carboxylates.[20]



Scheme 11

An example of the PRT concept applied to amines is seen in work by Undheim (Scheme 12).[21] In this example, an iodo-substituted benzyl group is used as the amine protecting group. The aryl radical formed by deiodination of the benzyl group (by SmI_2) abstracts a hydrogen alpha to the nitrogen. One-electron transfer from SmI_2 to the α-amino radical then affords an organosamarium species (a carbanion). These carbanions then underwent addition to a variety of carbonyl compounds, giving products of type **56**. The effectiveness of the abstraction (and hence, the yield of reaction) was highly dependent on the structure of the particular nitrogen heterocycle used. Therefore, the process is not general.

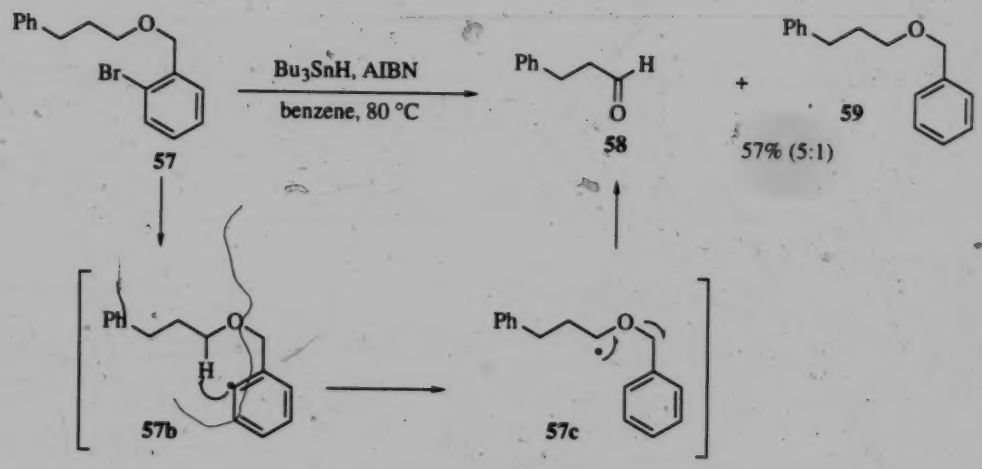
Replacing SmI_2 in the above reaction with Bu_3SnH allowed the α-amino radical to add to various alkenes, thus expanding the scope of the methodology.



54 **55** **56** (85%)

Scheme 12

Another example of the use of alcohol PRT groups is that shown in Scheme 13.[22] Unlike the phenyl protecting group employed earlier in Scheme 11, a benzyl ether has now been used (**57**).



57 **58** **59** 57% (5:1)

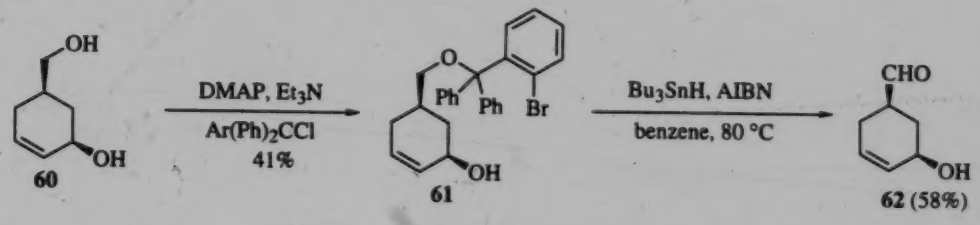
57b **57c**

Scheme 13

This is an important alteration, in the sense that the 1,5-H abstraction (**57** → **57b**) now results in a radical

situated alpha to the ether oxygen. With no group available for cyclization, the result is expulsion of a benzyl radical (**57c** → **58**). Thus, the major product recovered is aldehyde **58**. Compound **59** was also recovered as a minor product; it is produced from premature reduction of radical **57b** or **57c**. The net result of the process is a one-step deprotection-oxidation of a primary alcohol - a useful transformation in organic synthesis.

The same study included another useful application of this methodology (Scheme 14). The primary alcohol of diol **60** was protected selectively as a modified trityl ether. Upon exposure to tin radicals, the abstraction-expulsion sequence produced **62** in 58% yield. Thus, in a two step procedure, a primary alcohol has been oxidized in the presence of a reactive secondary allylic alcohol. One can envision this as a general method for the selective oxidation of primary alcohols in the presence of secondary alcohols.



Scheme 14

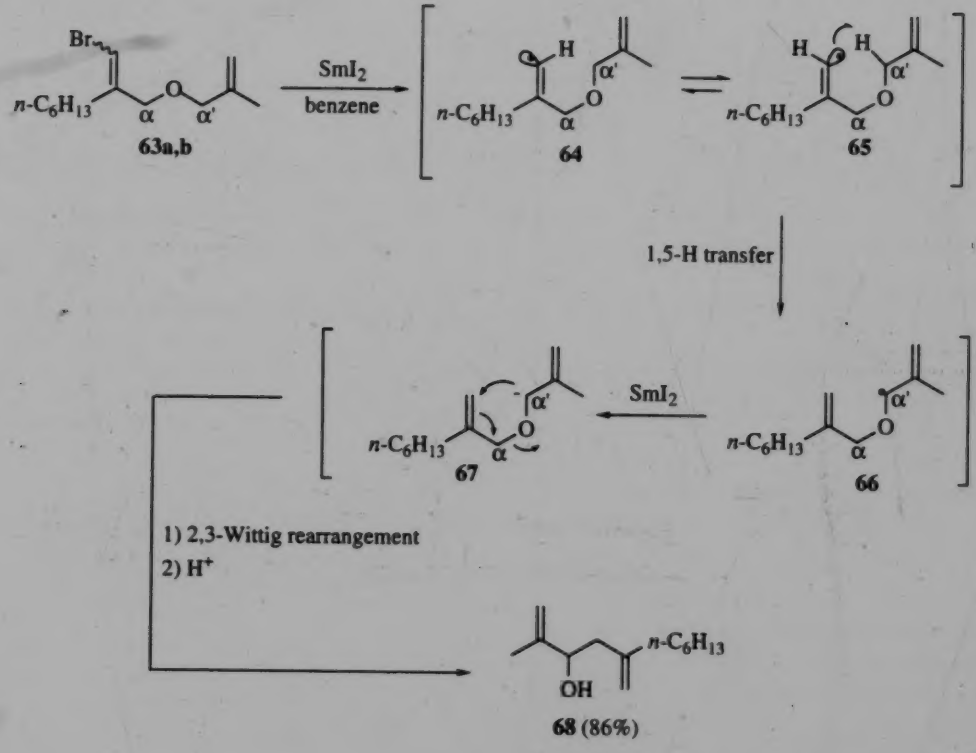
4b. Vinyl Radicals

Vinyl radicals are normally produced in one of two ways - by the cleavage of vinyl halides with tin radicals, or by

the addition of tin radicals to alkynes. They are also quite reactive and, as such, much of the literature dealing with hydrogen abstractions involves the use of these intermediates.

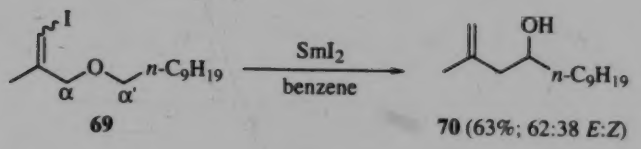
A beautiful example of the synthetic potential of 1,5-H transfer is seen in a study by Kunishima[23] on the Wittig rearrangements of unsymmetrical diallyl ethers (Scheme 15). Deprotonation of either the α or α' positions of **63a,b** with a base, such as BuLi, induces a 2,3-Wittig rearrangement. However, the ability to selectively generate a carbanion at either position is difficult, and is highly dependent on the structure of the substrate. This selectivity problem can be overcome by taking advantage of intramolecular 1,5-H abstractions. Reduction of vinyl bromides **63a,b** produced two possible isomeric vinyl radicals, **64** and **65**. Intermediate **64**, due to its geometry, cannot abstract hydrogen from the α' position. Therefore, the reaction is funneled through intermediate **65**, which has the proper geometry for 1,5-H abstraction (1,3-H abstraction from the α position is not a competitive side reaction). Radical **66** is then reduced to a carbanion with SmI_2 and, upon rearrangement, **68** is formed as a single isomer. Only traces of alkenes, from the direct reduction of radicals **65** and **66**, were detected. Upon substitution of THF for benzene as the solvent, more of the prematurely reduced products were observed, due to the superior α-H donating ability of THF. This work constitutes an efficient method for the selective metalation of

unsymmetrical diallyl ethers.



Scheme 15

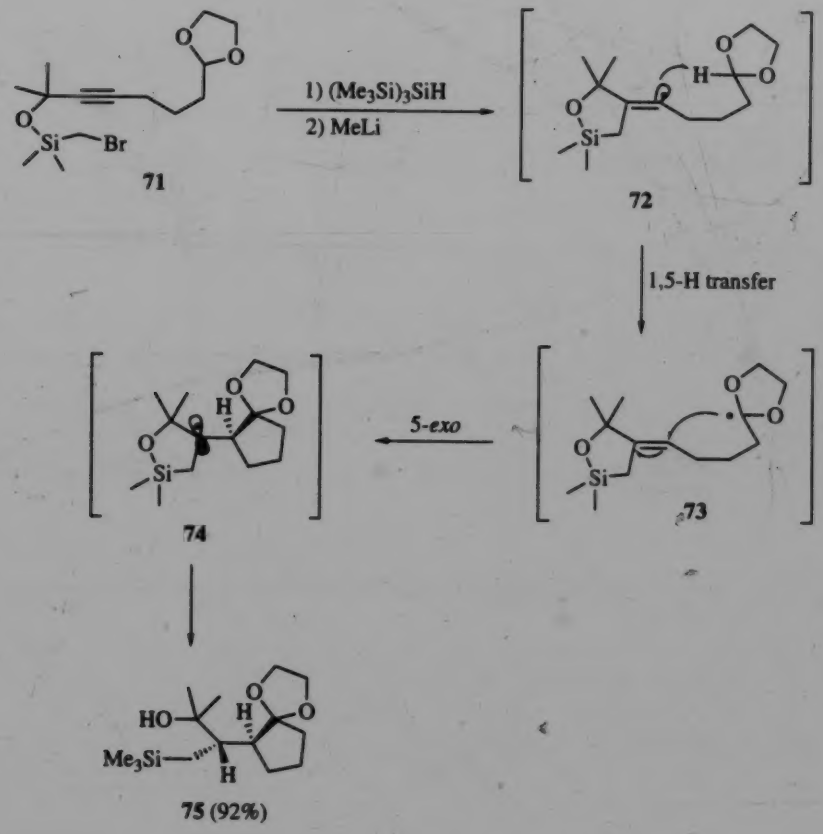
Another interesting example from the same group is shown in Scheme 16. Direct metalation of the α' position of **69** would be difficult, using a base, due to the lower acidity of the α' protons relative to the α protons. In this case, the 1,5-H transfer method allows selective carbanion formation at the α' position, giving **70** as a mixture of geometric isomers.



69 **70** (63%; 62:38 *E*:*Z*)

Scheme 16

Radical translocation of a vinyl radical has also been used nicely in a tandem process,[24] as shown in Scheme 17. Initial 5-*exo* cyclization of the radical derived from bromide **71** gave a vinyl radical intermediate (**72**).

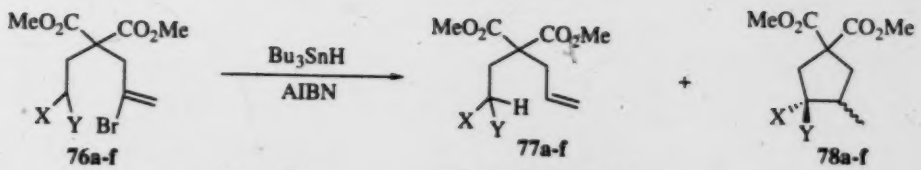


71 **72** **73** **74** **75** (92%)

Scheme 17

The acetal hydrogen was then abstracted by the vinyl radical (**72** → **73**), and the resulting 5-*exo* closure then proceeded stereoselectively, to give intermediate **74**. The bulk of the $(Me_3Si)_3SiH$ reagent,[25] as well as the conformation of **74**, allows the final radical quenching to proceed stereoselectively, and the result is a single diastereomer (**75**), produced in high yield. The use of Bu_3SnH as the hydrogen donor in this reaction resulted in the formation of some alkene side-products (by the direct reduction of vinyl radical **72**), due to the superior H-donating ability of Bu_3SnH with respect to $(Me_3Si)_3SiH$. These intermolecular hydrogen transfers are frequently observed to be competitive side reactions in 1,5 intramolecular processes.

In order to introduce a semblance of predictability to 1,5-H transfer reactions involving vinyl radicals, Curran performed a study,[26] in which he examined the effects of various functional groups on the efficiency of hydrogen abstractions (Scheme 19). Upon formation of a vinyl radical from **76a-f**, two possibilities exist: reduction by Bu_3SnH (to give **77a-f**), or 1,5-H abstraction, followed by rapid cyclization, to give **78a-f**. The ratio of cyclized to uncyclized products would be a reasonable measurement of the efficiency of the H-abstraction process. The results for a selected number of functional groups are given in the Scheme.



X	Y	uncyclized	cyclized
S-$(CH_2)_3$-S		<4	>96
CH_3	CH_3	13	87
CN	H	22	78
O-$(CH_2)_3$-O		33	67
O-CH_2		>96	<4
H	H	>96	<4

Scheme 19

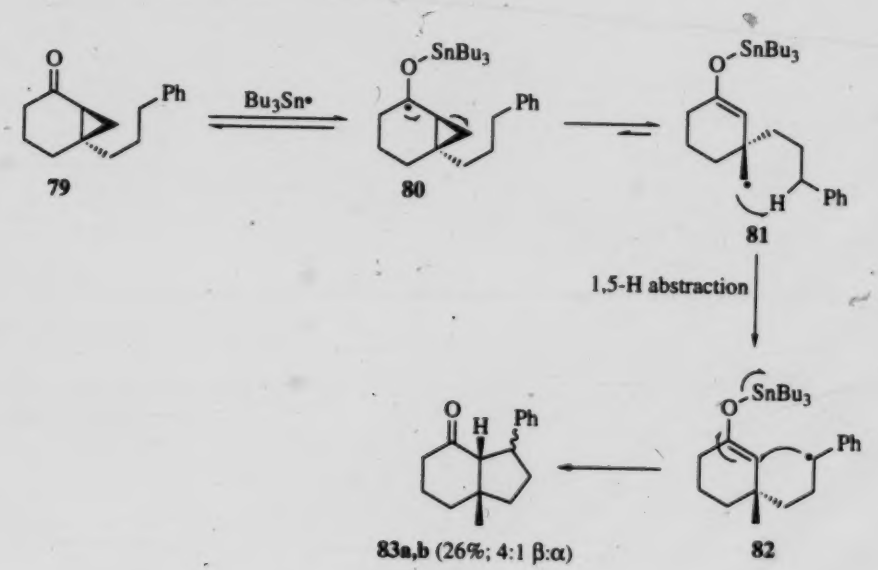
Some notable observations include the proficiency of the dithioacetal to promote H-abstraction, and the inability of epoxides and methyl groups (due to stronger C-H bonds) to do the same. While it is difficult to predict the effectiveness of any particular hydrogen abstraction process, this study does offer some guidelines when designing a synthesis based on radical translocation.

4c. Aliphatic Radicals

The design of a synthetic sequence based on radical translocation does not often attempt to utilize simple aliphatic carbon radicals. They are less reactive than their aryl or vinyl counterparts, and hence, are more subject to competitive side reactions, such as intermolecular hydrogen transfer.

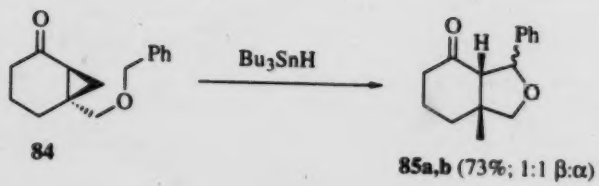
Rawal has shown that under certain conditions, alkyl radicals can be used efficiently in a 1,5-H transfer process (Scheme 20).[27] Cyclopropane fragmentation of radical **80**

produced methyl radical **81**, which then underwent a 1,5-H translocation (**81** → **82**) to give a more stable benzylic radical. Radical **82** then underwent a 5-*exo* closure onto the double bond, to give isomeric products **83a**,**b**, albeit in low yield. There were side products detected as well, the main ones being compounds formed by direct reduction (by Bu_3SnH) of alkyl radicals **81** and **82**.



Scheme 20

The yield was improved by performing the same reaction on a substrate such as **84** (Scheme 21). The 1,5-H abstraction, in this example, would be more efficient due to the stabilization of the resultant benzylic radical by the presence of the α-oxygen. Thus, 1,5-H abstraction by an aliphatic radical can be efficiently incorporated into a synthesis, provided a good H-donor site is available.

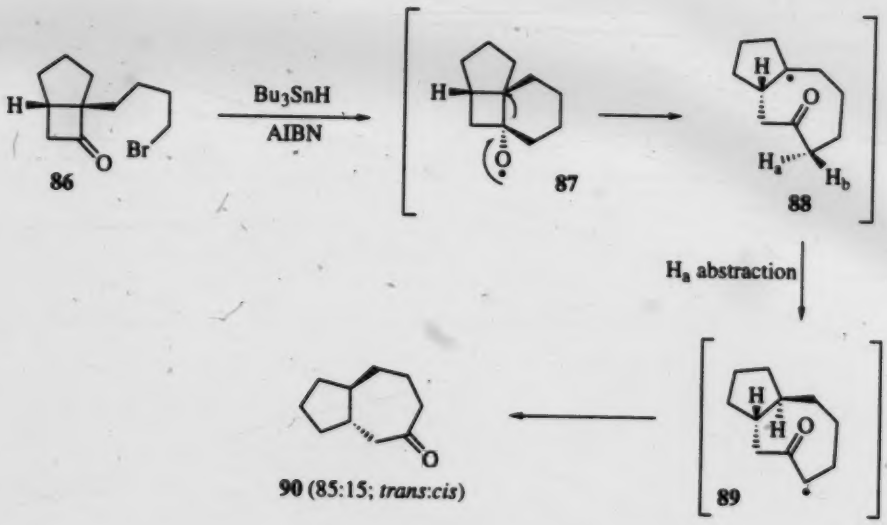


84 **85a,b** (73%; 1:1 β:α)

Scheme 21

It should also be noted that Rawal's analogous epoxide examples (*vide supra* - Scheme 4) result in higher yields than these cyclopropane cases. This is a direct result of the higher reactivity of alkoxy radicals relative to aliphatic radicals.

Dowd and co-workers have observed 1,5-H abstraction from an aliphatic radical in their work[28] on cyclization-fragmentation reactions (Scheme 22).



86 87 88 89 **90** (85:15; *trans*:*cis*)

Scheme 22

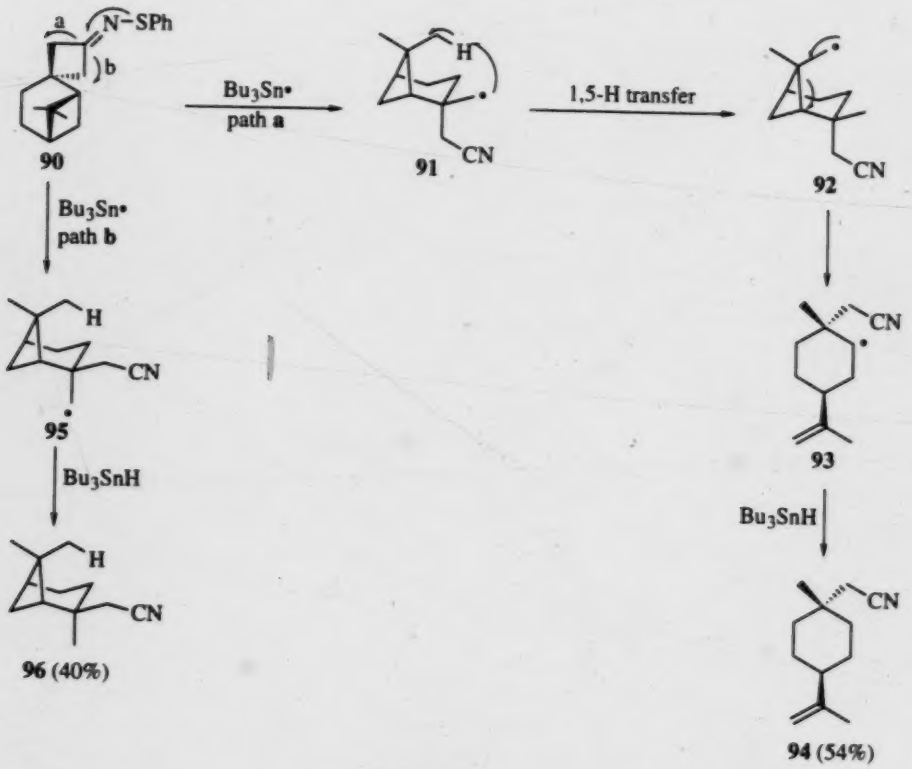
The aliphatic radical in intermediate **88** was formed by a

tandem sequence of radical addition to a carbonyl, followed by ring enlargement (**86** → **87** → **88**). Using deuterium studies, they showed that **88**, rather than being reduced intermolecularly by Bu_3SnH, was reduced by 1,5-H transfer. There was also a marked preference for the abstraction of H_a relative to H_b, and thus, the *trans*-fused bicyclic intermediate **89** was the major product isolated. The relatively stable α-keto radical **89** was then reduced by Bu_3SnH to give **90**.

The process was not general, as similar substrates did not undergo this intramolecular hydrogen abstraction, and more equitable distributions of *trans* and *cis* fused products were observed. The example in Scheme 22 does, however, demonstrate the potential ability of 1,5-H abstractions to control the stereochemical outcome of reactions. This application of intramolecular hydrogen abstraction has largely been ignored, but does hold promise in well-designed systems.

In Scheme 23, radical-induced fragmentation of the cyclobutane ring in **90** can occur via pathway **a** or **b**.[29] The geometry of intermediate radical **91** is such that a reasonable 1,5 hydrogen abstraction pathway exists, and thus, radical **92** is produced. Rapid cleavage of the strained ring system then gives, after reduction, compound **94**. The same hydrogen abstraction route is not available to radical **95**, due to the geometry of the system, and thus, this pathway leads to a product (**96**) of direct reduction. The 1,5-H translocation

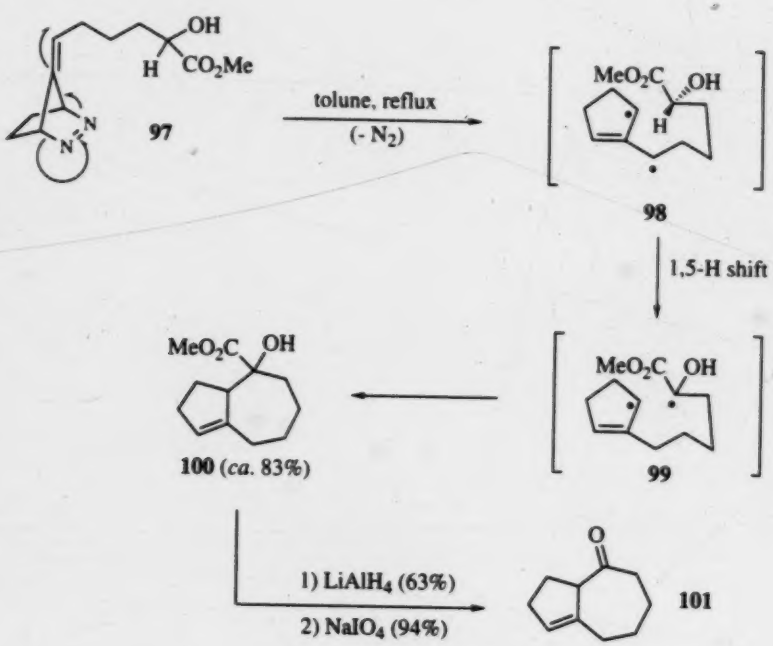
between two methyl radicals is rare, and only the rapid ring-cleavage following the abstraction allows it to proceed.



Scheme 23

One of the most interesting examples of 1,5-H abstraction emanating from an alkyl radical comes from a study by Little.[30] In this work, decomposition of the diazene **97** results in the formation of a trimethylenemethane diyl species **98**. Radicals such as **98** are often used to add to multiple bonds of other materials; however, under the proper conditions (*vide infra*), a 1,5-H abstraction can occur, to give diradical species **99**. Radical coupling (**99** → **100**) then completes formation of the bicyclic [5.3.0] ring system. The major side products (*ca.* 10%) in these reactions are

those resulting from dimerization of diyl **98**.



Scheme 24

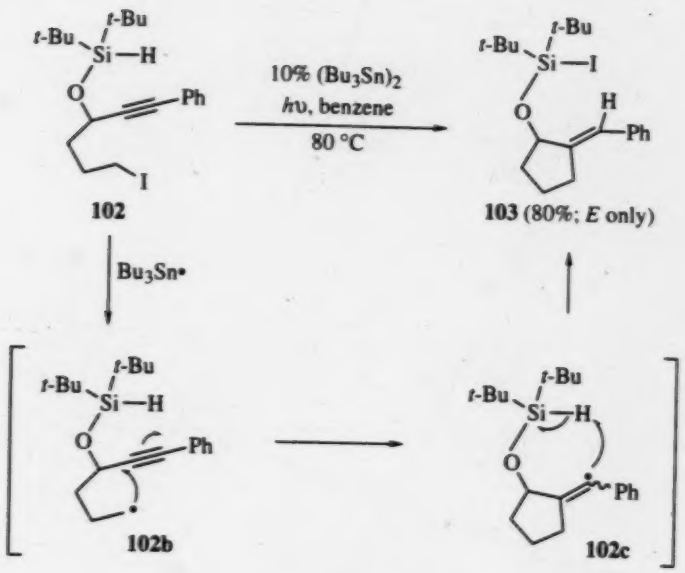
The choice of substituents on the carbon bearing the abstracted hydrogen atom is crucial. For example, the substituents (-OH, -CO_2Me) in Scheme 24 were chosen in order to take advantage of the captodative (push-pull) stabilizing effect. The hydrogen abstraction only took place in systems in which the bond strength of the appropriate C-H bond was below 90 kcal/mol. Therefore, by simply calculating these bond strengths, the authors could predict how well each substrate would perform. For cases in which the bond strength was too high, the product arising from diyl dimerization was the only one detected.

5. Hydrogen Abstraction from Silicon

The chemistry in the preceding part of this review has involved hydrogen abstractions from carbon. A relatively unexplored area, which is just now gaining attention, are procedures which employ silicon hydrides as the hydrogen donor. An important contribution in this area has been introduced by this laboratory - the details of this work will be discussed in the results section of Chapter 2. Some other examples of the utility of silicon hydrides are given below.

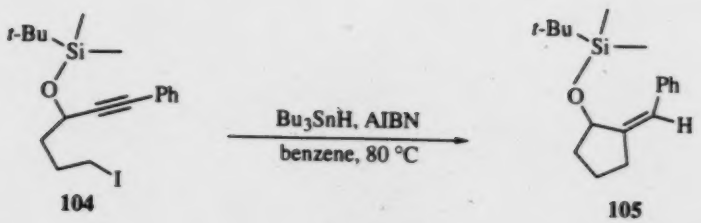
The majority of cases in the literature dealing with 1,5 hydrogen abstraction, involve a cyclization or an addition, following the radical translocation step. It was seen earlier (Scheme 22) that intramolecular hydrogen abstraction can also be used to control the stereochemical outcome of reactions.

This strategy was used by Curran in the development of a method for the stereoselective synthesis of alkenes (Scheme 25).[31] His procedure is related to the earlier work done in this laboratory. The 5-*exo* closure of radical **102b** (produced from iodide **102**), gave a vinyl radical (**102c**) of mixed geometry. Intramolecular abstraction of the silicon hydride occurred in a stereoselective manner, giving **103**, as the *E*-isomer exclusively. The silicon radical produced in the final step abstracts iodine from another molecule of **102**, to continue the chain, and to give **103**. Thus, the geometry of the alkene is strictly controlled by the intramolecular hydrogen transfer step.



Scheme 25

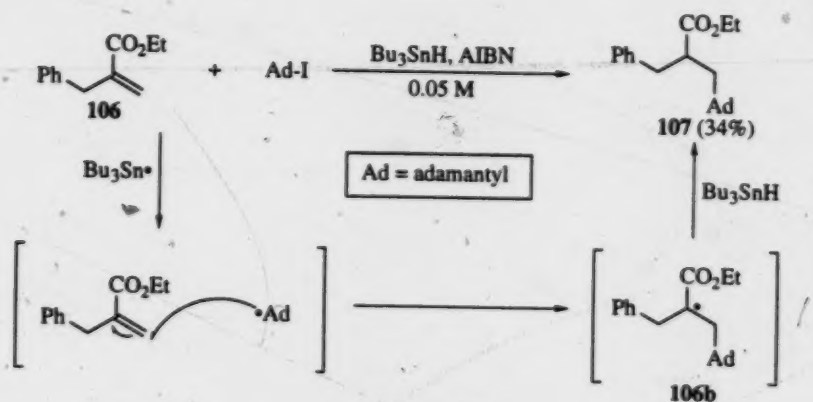
The same reaction was performed on compound **104**, in which a TBDMS ether had replaced the silicon hydride of **102**. In this case, *Z*-alkene **105** (Scheme 26) was produced almost exclusively (95:5 *Z*:*E*). In the absence of a suitably placed silicon hydride, the intermediate vinyl radical, generated in the penultimate step, must be quenched externally by Bu_3SnH, and this would occur predominantly on the side opposite to the bulky TBDMS group. These results demonstrate the ability of intramolecular hydrogen abstraction to control the stereochemical outcome of a reaction. The procedures in Schemes 25 and 26 complement each other, as either alkene geometry can be obtained.



104 105

Scheme 26

Another recent application of silicon hydride abstraction involves attempts to improve the efficiency of bimolecular radical additions.[32] Some of the problems associated with bimolecular radical reactions are illustrated by the example in Scheme 27 - addition of an adamantyl radical to the double bond of α,β-unsaturated ester **106**. The desired product **107** is formed, but in low yield. Reaction conditions for bimolecular radical additions must be carefully controlled, in order to make the process efficient. Certain factors must be considered when attempting the reactions.

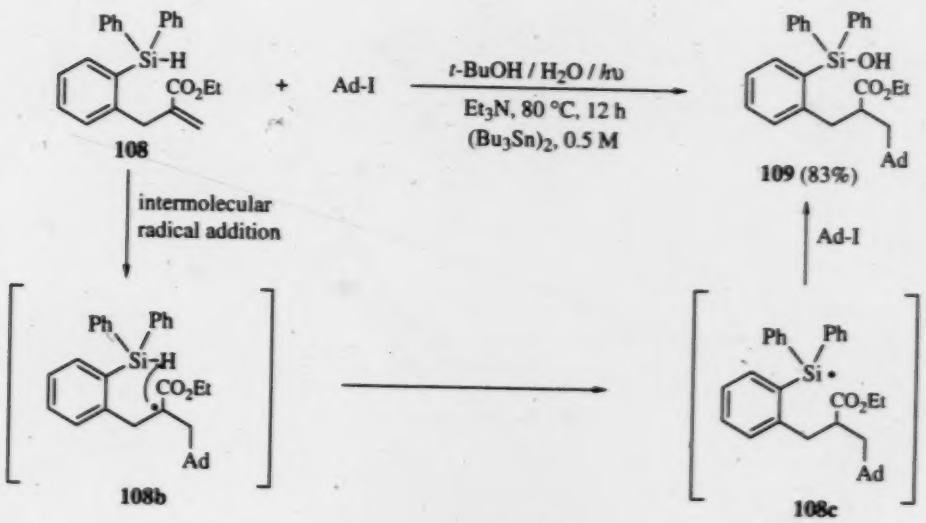


Scheme 27

First, the bimolecular radical addition (to form **106b**) is slow, compared to an intramolecular cyclization. Therefore, the adamantyl radical must have a significant lifetime in order to add intermolecularly before being quenched. In practice, this is done by minimizing the concentration of the metal hydride (by slow addition of hydride or by high dilution), and maximizing the concentration of alkene (by using excess alkene). Neither of these conditions were met in the example of Scheme 27; the concentration of the reaction mixture (0.05 M) was too high, and only one equivalent of alkene was present. Secondly, it is sometimes difficult to establish selectivity between the initial and adduct radicals. Selectivity is critical because the initial and adduct radicals must react in a different manner; the initial radical must add intermolecularly, while the adduct radical must propagate the chain. In practice, this is overcome by designing a reaction in which structurally different initial and adduct radicals are involved (e.g. the adamantyl radical and radical **106b** in Scheme 27).

Similar conditions, as those in Scheme 27, were used for the reaction involving substrate **108** (Scheme 28), which is identical to **106**, with the exception of the presence of a silicon hydride moiety attached to the phenyl ring. The yield in this case is much improved. One feature of Scheme 28 that differentiates it from Scheme 27 is the 1,5 intramolecular hydrogen abstraction (**108b** → **108c**), which

follows the initial bimolecular addition. The chain propagating step is also different; abstraction of an iodide, from Ad-I, allows the chain to continue. The presence of water in the reaction mixture allows the resulting unstable silicon iodide to be converted *in situ* to the corresponding silanol **109**.

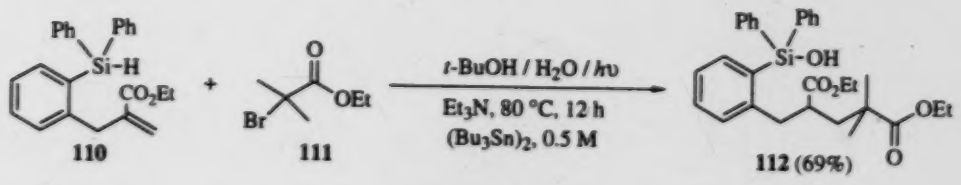


Scheme 28

There are several advantages to this unimolecular chain transfer reaction. First, regardless of the structure of the starting material, the initial and adduct radicals are differentiated, in that the adduct radical has a rapid intramolecular option (1,5-H abstraction) that is not available to the initial adamantyl radical. Secondly, the metal hydride can be used catalytically. In the first example (Scheme 27), a full equivalent of tin was used, due to the fact that the chain transfer step (**106b** → **107**) is

slow. In Scheme 28, the abstraction of an iodide by a silicon radical is relatively fast. Therefore, the chain is propagated efficiently. Finally, careful control of reaction conditions is unnecessary - even in cases of high concentration and stoichiometric ratios of reagents, good yields are obtained. In Scheme 28, the high concentration (0.5 M) and the use of a single equivalent of alkene **108**, does not hinder the reaction.

The benefits of the unimolecular chain transfer method are further illustrated in Scheme 29. A good yield of the desired product (**112**) was obtained. This particular transformation would be very difficult to achieve efficiently by using the standard intermolecular radical addition conditions. This is due to the fact that both the initial and adduct radicals are tertiary radicals, positioned alpha to an ester. Thus, there is no differentiation between them in the standard intermolecular case. In the unimolecular chain transfer case of Scheme 29, only the adduct radical has a 1,5 hydrogen abstraction pathway; this is where the selectivity occurs. Superior yields were obtained for a number of substrates. Thus, this modification represents a promising contribution to intermolecular radical reactions.



Scheme 29

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RESULTS AND DISCUSSION

1. Introduction

Prostaglandins and their analogues are some of the most widely studied natural products in science. They are widely distributed in mammalian tissues and exhibit a considerable range of biological activity. The amount of literature that deals with these pharmacological aspects is vast.[1] The compounds shown in Figure II-1 are just a few of the many different types of prostaglandins that are known. Although each individual prostaglandin is unique in structure, the similarities between the compounds are evident.

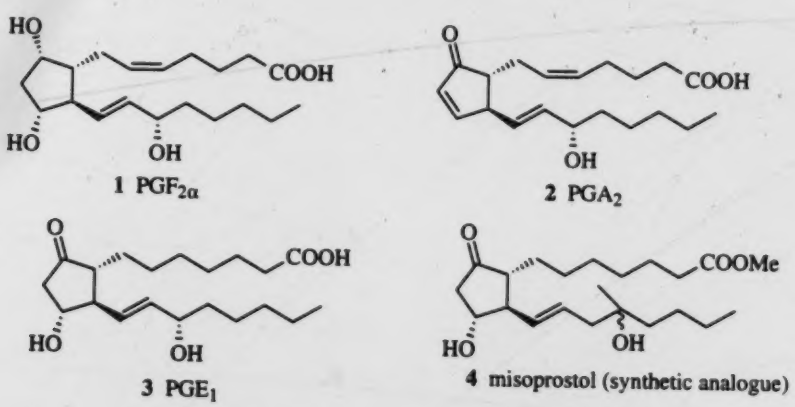
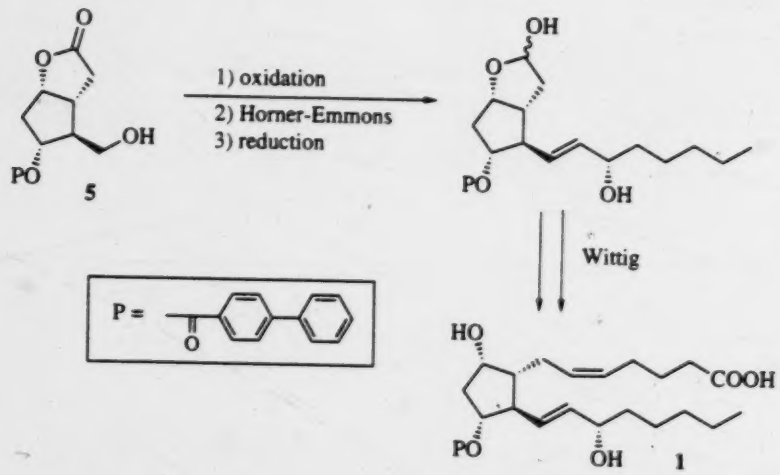


Figure II-1 - Some Natural and Synthetic Prostaglandins

The two general structural features are the substituted cyclopentane ring and the two carbon chains. Along with the vast amount of literature concerned with the biological aspects, there is an impressive body of work that describes synthetic approaches to these compounds.[1] Because of their

closely related structures, one specific synthetic approach can provide access to numerous different prostaglandins. The prostaglandins themselves can even be interconverted by simple chemical transformations.

If one considers control of stereochemistry to be a central factor in natural product synthesis, then $PGF_{2\alpha}$, with five chiral carbons, can be considered the most challenging prostaglandin to synthesize. Since the initial synthesis of $PGF_{2\alpha}$ by Corey,[2] a general strategy has emerged for the synthesis of this particular prostaglandin, and for others as well.



Scheme 1 - General Strategy for Conversion of Corey Lactone (5) into $PGF_{2\alpha}$ (1)

The lactone intermediate which Corey had used would later become known as the Corey lactone (**5** in Scheme 1). This often became the initial target for research groups, with the side chains then being attached by Wittig or Wittig-type reactions.[2] The synthesis of the Corey lactone or a

closely-related compound would then constitute a formal synthesis of $PGF_{2\alpha}$.

One advantage of this strategy is the opportunity to prepare a series of analogues with subtle alterations in the side chains, via a common intermediate. The side chains are the main site of metabolism in prostaglandins,[1] and therefore, subtle changes in these parts of the molecule could lead to analogues with enhanced biological activity (e.g. misoprostol in Figure II-1). The obvious challenge in a synthesis of the Corey lactone is the construction of a five-membered ring containing four contiguous stereocenters. Free-radical reactions are very proficient in the construction of cyclopentanes and so we wished to develop a strategy for making the Corey lactone based on a type of tandem radical process first reported from this laboratory.

2. Cyclopentane Formation using 1,5-Hydrogen Transfer

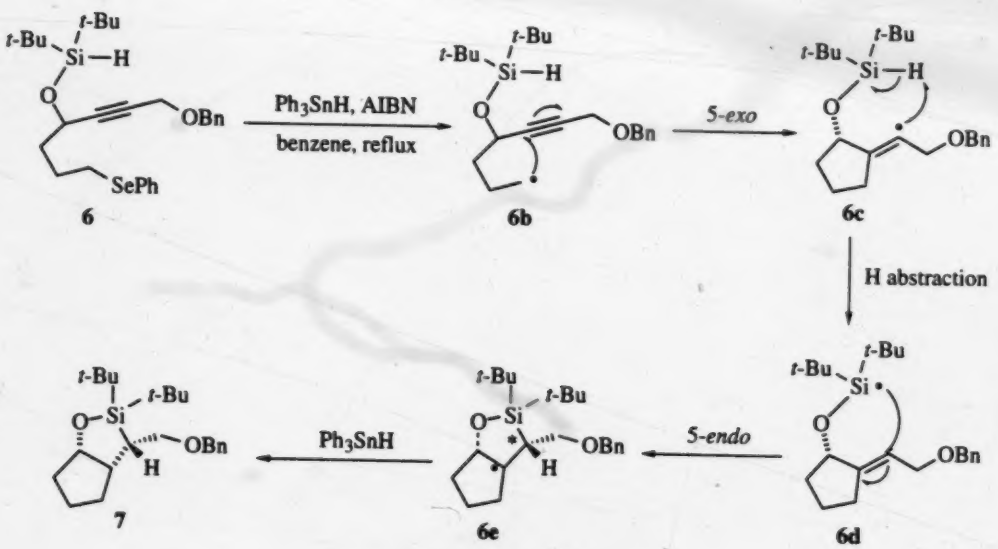
The key strategy we planned to use in our approach to the Corey lactone is based on some chemistry that was developed a short time ago in our group. This work involves a method of making substituted cyclopentane rings in a stereocontrolled manner.[3] Scheme 2 summarizes the stages of this tandem radical cyclization, and a detailed discussion of the mechanism is in order at this point.

An appropriate substrate for this reaction is a compound such as **6**, which contains three necessary features:

a) a radical precursor - here, a phenylselenide was used but any other radical precursor could presumably be used

b) a radical acceptor in the form of a triple bond - a triple bond is necessary in order to accommodate TWO cyclizations

c) a suitably placed silicon hydride, which will act as a hydrogen donor AND a center for radical cyclization.



Scheme 2 - Tandem Radical Cyclization

The initial step in the sequence is a tin-mediated cleavage of the PhSe group to generate an alkyl radical **6b**. Standard 5-*exo-dig* closure onto the triple bond results in the formation of a 5-membered ring along with a highly reactive vinyl radical. Hydrogen abstraction from silicon by this vinyl radical then generates silicon radical **6d**, which undergoes 5-*endo* cyclization onto the alkene unit to generate

yet another radical (**6•**). Two features of this particular 5-*endo* closure deserve mention here. First of all, 5-*endo* radical closures are normally disfavored by Baldwin's rules[4] because severe distortions in bond angles and lengths are necessary for the molecule to adopt an appropriate conformation for cyclization. However, the relatively large bond length of the developing C-Si bond in this case lowers the energy barrier to cyclization. Other examples of 5-*endo* closures involving a silicon-containing ring have been reported.[5] The second feature of this step is that the ring closure occurs stereoselectively, forming a new asymmetric center in the process (denoted by an asterisk in **6•**). For our purposes, this is inconsequential as the stereochemistry at this carbon will be destroyed later in our synthesis. The final step in the sequence is the quenching of the intermediate tertiary radical **6•** by Ph_3SnH exclusively from the top face of the molecule to generate another stereocenter. The final compound type produced from this model study is a cyclopentane ring with 1,2-*cis* substituents (**7**). Since all stereochemistry is controlled by a single carbon center, this process could potentially be used in the synthesis of enantiomerically pure compounds (by starting with an optically active alcohol).

3. 11-Deoxyprostaglandins

11-Deoxyprostaglandins, as their name suggests, are simply analogues of the naturally occurring prostaglandins

lacking a hydroxyl group at C(11) (see numbering scheme in Figure II-2). Like the parent compounds, they exhibit a wide range of biological activity, and in some cases, the activity is higher than the parent prostaglandin. From a synthetic chemistry standpoint, they are easier to make, and so provide a good model system to test certain synthetic strategies. We decided to evaluate our approach on these simpler compounds by attempting a synthesis of 11-deoxy Corey lactone (**9** in Scheme 3)

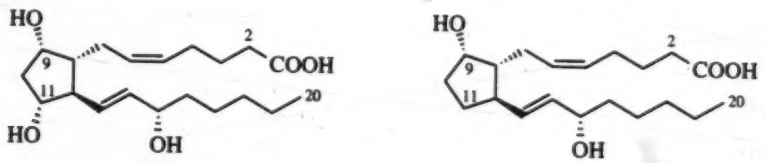
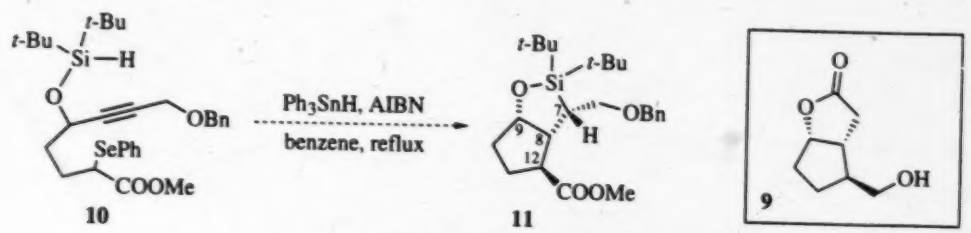


Figure II-2 - $PGF_{2\alpha}$ (1) and 11-deoxy $PGF_{2\alpha}$ (8)

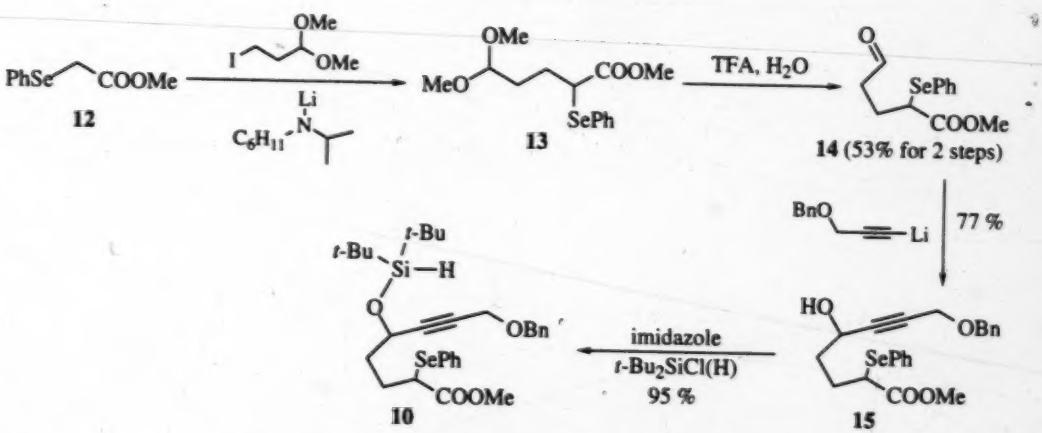
Our strategy to synthesize **9** is summarized in Scheme 3. We envisioned a simple alteration of the original model compound **6** by attaching an ester substituent adjacent to the selenide-bearing carbon, so as to get compound **10**. If cyclization were to take place as it had in the earlier model, compound **11** would be obtained. In compound **11**, the stereochemistries at C(7), C(8), and C(9) (numbering scheme corresponds to $PGF_{2\alpha}$ numbering) would be determined by the mechanistic pathway of the reaction, while the *trans* stereochemistry at C(12) would have to be governed by steric factors. The similarities between compound **11** and 11-deoxy Corey lactone (**9**) are evident and therefore we did not

anticipate any major problems in the conversion of **11** into **9**. In order to test the feasibility of our approach, we needed to make compound **10**.



Scheme 3 - Strategy for 11-deoxy Corey Lactone Synthesis

The first step in the route to compound **10** was the alkylation of methyl (phenylseleno)acetate (Scheme 4). Our initial attempts at this alkylation (using LDA as the base) were not successful; we observed only traces of **13** in the ^1H NMR spectrum.

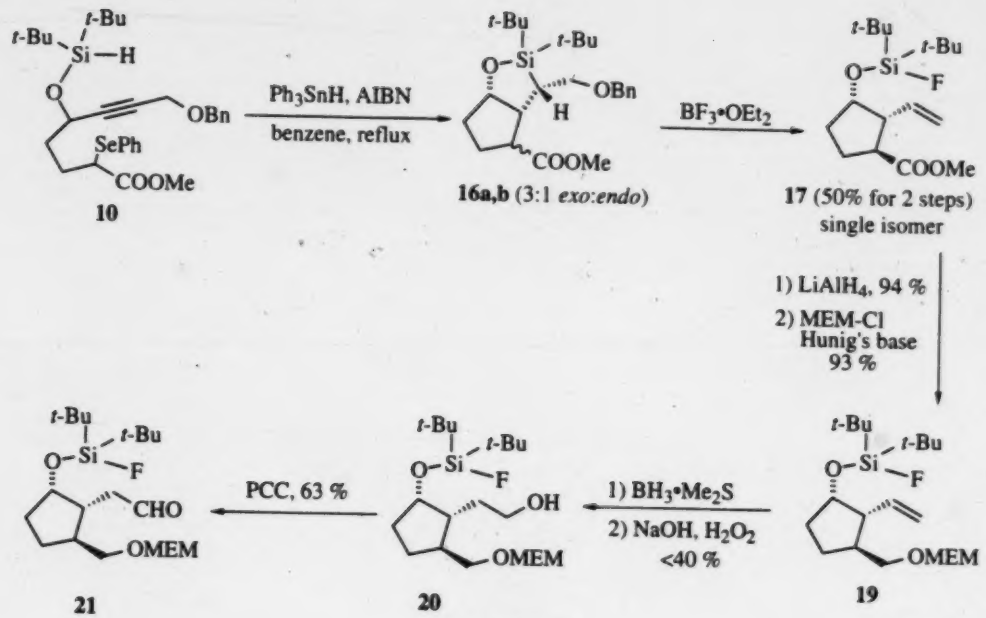


Scheme 4 - Synthesis of Radical Cyclization Precursor 10

We were eventually successful by closely following

Rathke's alkylation procedure.[6] Hydrolysis of the resulting acetal[7] occurred smoothly, to give aldehyde **14**. Conversion to the propargylic alcohol **15** was accomplished by the use of the lithium anion of benzyl propargyl ether. Finally, silylation of this alcohol gave us substrate **10**.

The tandem radical reaction proceeded as we had envisioned (Scheme 5), giving a mixture of diastereomers **16a,b** in a *ca.* 3:1 ratio (the ratio was determined by analysis of the ^{1}H NMR spectrum). At this point, we could not determine if the desired *exo* isomer was indeed the major compound. Based on steric considerations though, we suspected as much, and so proceeded on this assumption. The inseparability by chromatography of compounds **16a** and **16b**, as well as the presence of tin residues in the mixture, precluded full characterization. This problem was rectified in the subsequent step, in which a single diastereomer **17** was obtained and fully characterized. The double bond in **17** was produced in a Peterson-type process.[8] Thus, fluoride attack on silicon is accompanied by double bond formation as well as expulsion of the -OBn moiety. The minor epimer was presumably produced in the reaction as well (there were a few other minor spots detected by TLC). However, we did not isolate it; we simply proceeded with the major compound, which we assumed had the required stereochemistry. The oxygen functionality (in the form of the -OBn group) was lost; it was, however, required, and we felt that it could easily be re-installed later by hydroboration.

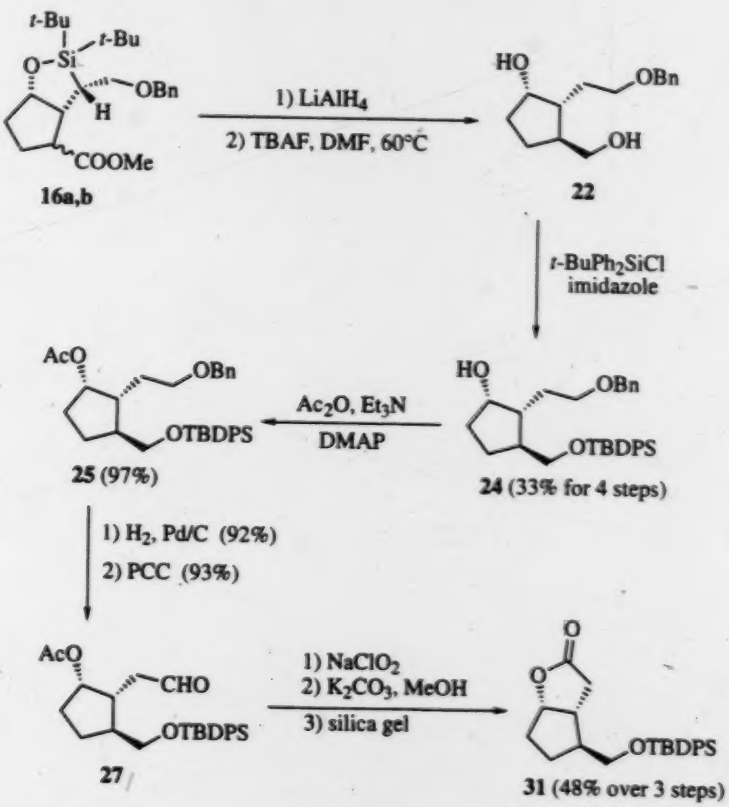


Scheme 5

Also, at the time, this was the only efficient method we knew for breaking the C-Si bond (alkyl silanes are much more difficult to cleave than allyl or vinyl silanes).[9] For example, simply treating **16a,b** with TBAF at room temperature resulted in cleavage of the O-Si bond but did not affect the C-Si bond.

Regardless, we proceeded with LAH reduction and protection (MEM-Cl, *i*-Pr_2NEt) of the resulting alcohol, to give **19**. It was at this point that the hydroboration reaction was used to re-install the oxygen functionality. Unfortunately, low yields were obtained, and all attempts to raise the yield to an acceptable level were unsuccessful. We proceeded with the synthesis as far as aldehyde **21**. We felt

that it should be possible to convert **21** easily into 11-deoxy Corey lactone - all that was required was formation of a lactone and deprotection. However, the low yield in the hydroboration was troubling enough that we decided to re-examine the step in which the C-Si bond was cleaved. Specifically, we wanted to find a method that would cleave this bond and retain the oxygen functionality. We were able to find such a procedure in the form of a protodesilylation reaction that had been developed by Stork,[10] and subsequently used by other groups for similar purposes.[11]



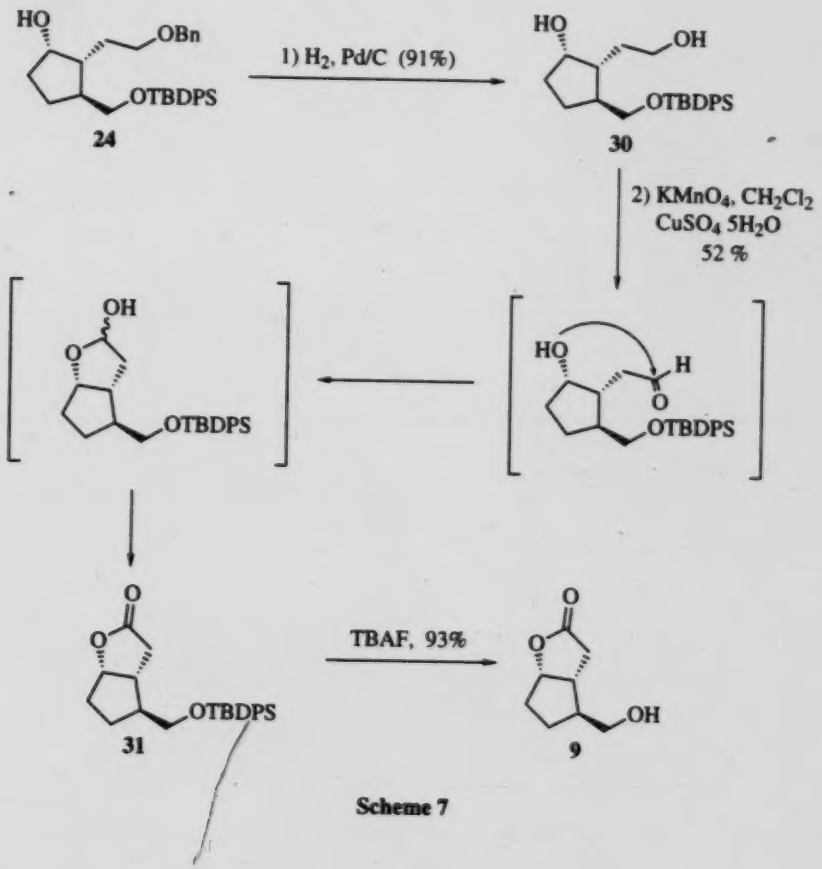
Scheme 6

Reduction of diastereomers **16a,b** ($LiAlH_4$), followed by treatment with TBAF in DMF at 60 °C, resulted in both C-Si and O-Si bond cleavage - with retention of the oxygen functionality (Scheme 6). It was not clear why these particular conditions were successful, and no rationalizations were given in the original paper. Rather than study the reaction (e.g. by changing temperatures and solvents) to determine the necessary conditions for C-Si bond cleavage, we just exploited it for our own purposes, and proceeded with the sequence. Selective protection of the primary alcohol (TBDPS-Cl)[12] afforded the advanced intermediate **24**. It should be noted here that a completely pure compound could not be obtained in this sequence until we reached **24**; hence, the yield is quoted over four steps. The somewhat moderate yield for this sequence is offset by the fact that the basic skeleton of the 11-deoxy Corey lactone has been constructed with correct stereochemistry at the appropriate positions.

A number of standard chemical reactions completed the synthesis. The secondary alcohol was first protected by acetylation. Removal of the benzyl group, as well as oxidation of the resulting alcohol ($CH_2OH \rightarrow CHO \rightarrow COOH$), gave a carboxylic acid. Acetate hydrolysis and acidification (silica gel) then resulted in lactone formation (**31**).

The sequence could be shortened somewhat (Scheme 7) by taking compound **24** and immediately removing the benzyl group to give 1,4-diol **30**. Lactonization then occurred upon

treatment with $KMnO_4$ and $CuSO_4 \cdot 5H_2O$. These oxidation conditions[13] were found to be selective for primary alcohols over secondary alcohols, and in the specific case of 1,4-diols, were found to produce lactones efficiently. The sequence leading to lactonization (Scheme 7) is a) selective oxidation of the primary alcohol to an aldehyde, b) cyclization to form a mixture of lactols, and c) oxidation to the lactone. Finally, deprotection gave compound **9**, whose stereochemistry was confirmed by comparison to published spectral data.[14]

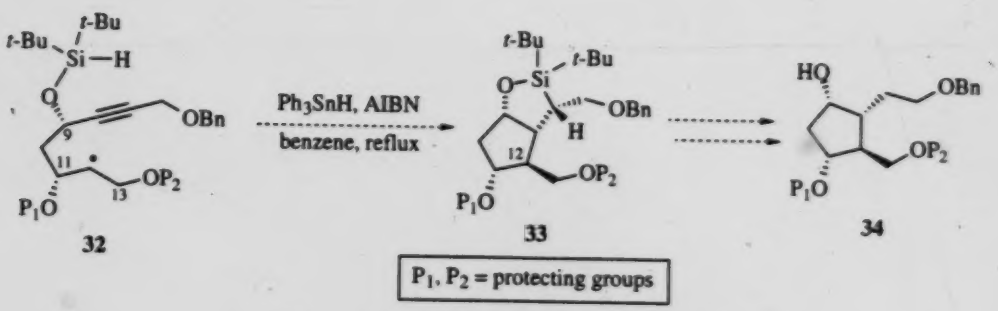


Scheme 7

4. Synthetic Approaches to the Corey Lactone

4.1 General Considerations

With a relatively efficient synthesis of 11-deoxy Corey lactone completed, our attention turned to the somewhat more complex Corey lactone **5**. Since the tandem radical cyclization would again be our critical step, we required a substrate which could generate a radical intermediate of type **32** (Scheme 8). The key additional feature of **32** is the presence of a protected C(11) hydroxyl group. The oxygen functionality at C(13) is shown as a protected alcohol but is not limited to this moiety; an aldehyde or ester would be just as suitable. One final feature of **32** to consider is that the *syn* relationship of the C(9) and C(11) hydroxyl groups should ideally be set prior to cyclization.



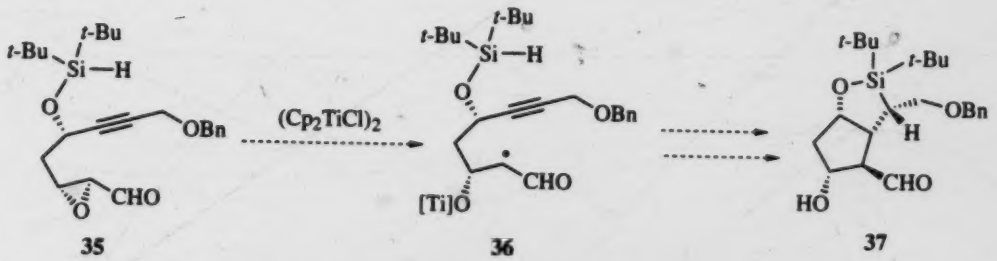
Scheme 8 - General Approach to Corey Lactone

Upon cyclization of **32**, intermediate **33** would be obtained, provided the stereochemistry at C(12) would again be controlled by steric factors. We expected this to be the case because of the success we had had in making the 11-deoxy

Corey lactone. Furthermore, with the additional C(11) hydroxyl present, it was possible that the stereocontrol would be even more biased towards the desired compound. Completion of the synthesis (**33** → **34** → **5**) would be done analogously to our earlier studies.

4.2 Our First Approach - Use of Epoxides

In our first approach to the Corey lactone, we attempted to take advantage of the regioselective epoxide opening that can be achieved using $(Cp_2TiCl)_2$. This reagent was discussed in Chapter 1; it cleaves epoxide bonds regioselectively[15] by a radical process, such that the more stable of the two possible radicals is produced. In order to use this reagent, we required a substrate such as **35**.



35 **36** **37**

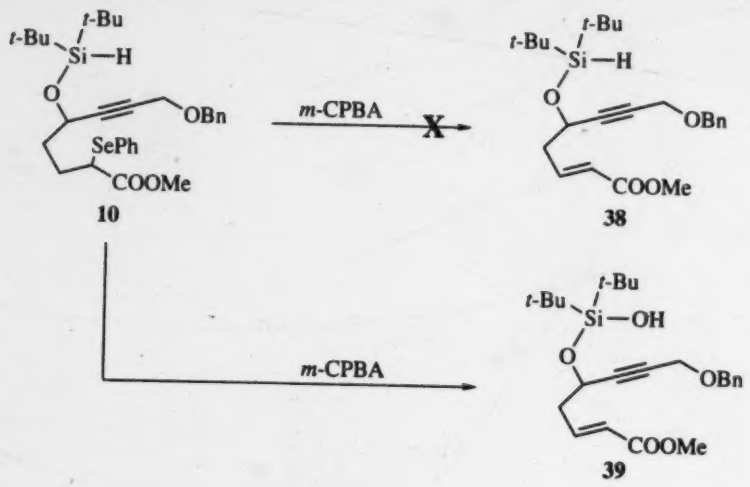
Scheme 9 - Possible Use of Epoxides in Tandem Cyclizations

If **35** were to be treated with the titanium reagent, cleavage of either bond of the epoxide would produce secondary radicals, but one of these radicals (**36**) would be stabilized by the adjacent aldehyde moiety. Our hope was

that this stabilization would be sufficient to promote selective epoxide opening in the manner shown (**35** → **36**). If the tandem cyclization reaction were to then proceed from this initial radical, compound **37** would be obtained.

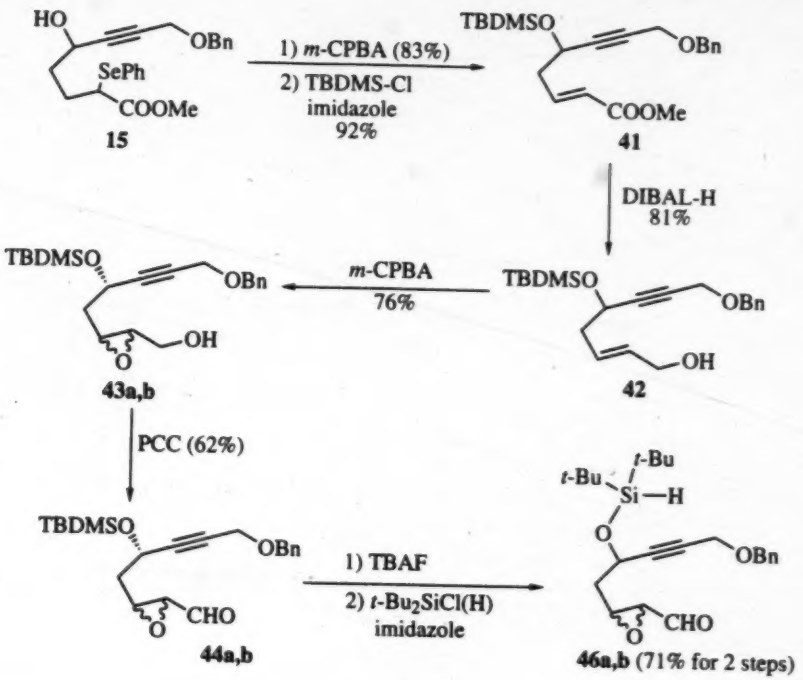
Conversion to the Corey lactone could then be accomplished by the sequence we had used for the 11-deoxy Corey lactone. None of the examples in the original RajanBabu paper involved discrimination between two secondary radicals. In all cases, the epoxide opening was inherently biased (e.g. secondary vs. primary or tertiary vs. primary radicals). Therefore, we had to test the validity of our expectations, and we set out to make a compound of type **35**.

We immediately recognized that we might be able to gain rapid access to a compound of type **35** by using **10** (Scheme 10) as the starting material. With **10** already available from our work on 11-deoxy prostaglandins, we attempted to carry out a selenoxide elimination[16] with *m*-CPBA (**10** → **38**, Scheme 10) in order to generate a double bond which could later be epoxidized. Elimination of the selenide in **10** (via the selenoxide) indeed occurred smoothly but was also accompanied by conversion of the Si-H unit to a Si-OH group (**10** → **39**). This unwanted transformation would hinder us again, later on in our studies (*vide infra*).



Scheme 10

We were not aware of any literature precedents for this conversion but, in any case, we had to change the approach slightly, since the Si-H moiety was required in the cyclization substrate. The obvious solution was to start with alcohol **15** (Scheme 11) which was also available from our earlier studies. Elimination of the selenide with *m*-CPBA (via the selenoxide), followed by alcohol protection (TBDMS-Cl), gave the α,β-unsaturated ester **41**. DIBAL reduction produced allylic alcohol **42**, and epoxidation then gave a mixture of inseparable epoxides **43a,b**. Oxidation of the free hydroxyl group (PCC) took us as far as **44a,b**. Finally, deprotection of the secondary alcohol, followed by installation of the silane, gave us a suitable substrate (**46a,b**) to test our proposed radical cyclization.

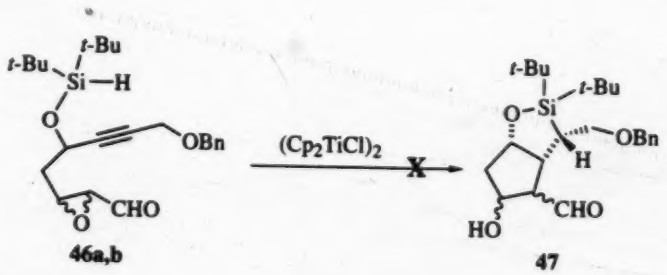


Scheme 11

In Scheme 11, there are two points that require comment. First of all, a potentially faster route to a radical cyclization precursor would involve epoxidation of α,β-unsaturated ester **41**, using one of the common literature methods available for this process.[17] We chose to take the three-step route to epoxy aldehydes **44a,b** for two reasons: 1) in general, epoxidation of allylic alcohols is easier than that of α,β-unsaturated esters, and 2) we felt that the greater electron withdrawing ability of the aldehyde (compared to the ester) would aid in the selective cleavage of the epoxide. Another important point concerns the stereochemistry of epoxides **46a,b**. The fact that there

exists a pair of diastereomers at this stage means that if the tandem cyclization were to take place as planned, we would potentially obtain four different products. This is not an ideal situation, but we felt that we could still gain some valuable information by attempting the experiment. If we observed signals corresponding to compounds of type **47** (Scheme 12) in the NMR spectrum, then we would be confident that the reaction was feasible; only then would we deal with the problem of setting the epoxide stereochemistry correctly.

Unfortunately, the results of the radical cyclization were not promising (Scheme 12). Examination of the reaction mixture by TLC revealed a streak covering almost the full length of the plate; no distinct spots were present. Secondly, we observed no signals in the ^1H NMR spectrum of the crude product, to suggest that compounds of type **47** had been formed.



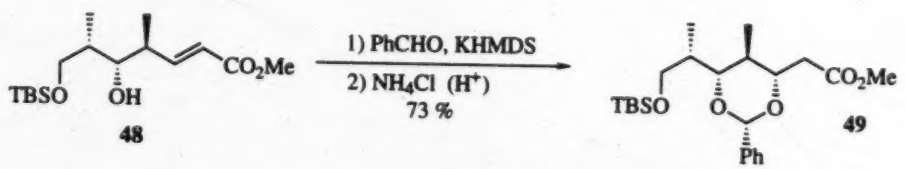
Scheme 12

It was not clear why the reaction had not worked, and we decided to end our studies in this particular area and move on to a new approach.

4.3 Formation of 1,3-diols via Cyclic Carbonates or Acetals

Before undertaking our new approach to the Corey lactone, we decided that, as a general requirement, the *syn* relationship between the C(9) and C(11) (prostaglandin numbering scheme) oxygen functionalities should be set early in the sequence. This would prevent the possibility of multiple product formation when we eventually attempted the radical tandem reaction.

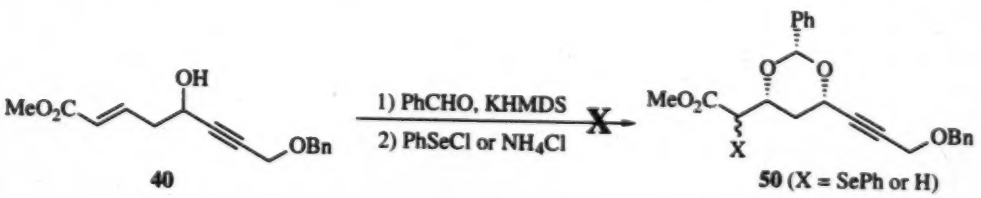
As a result, our immediate objective became the formation of compounds containing the *syn*-1,3-diol subunit. In our initial foray into this area, we adopted a procedure that Schreiber had used (Scheme 13). In that work,[18] the free hydroxyl of compound **48** added to benzaldehyde under basic conditions. The intermediate hemiacetal then underwent an internal Michael addition to the α,β-unsaturated ester moiety to give benzylidene acetal **49**. The



Scheme 13 - Schreiber Method of Forming 1,3-diols

noteworthy feature of this reaction is that the Michael addition proceeded with complete stereoselectivity - no trace of the *anti*-1,3-diol derivative was detected. We felt that under similar conditions, compound **40** (Scheme 14), available

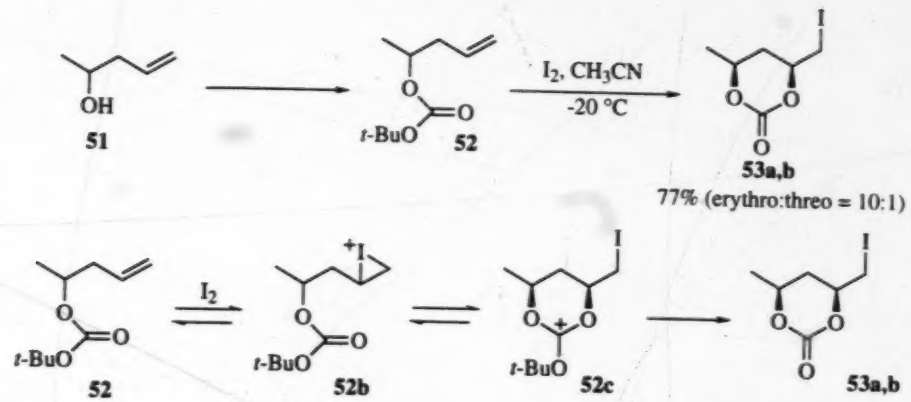
to us from the previous section, would undergo the same reaction. Furthermore, if we were to quench the reaction with PhSeCl rather than acid, the radical precursor would be installed in the same step. We could then transform **50** into an appropriate substrate for radical cyclization. With **40** already in hand, we immediately tested the reaction using Schreiber's conditions, but had no success in obtaining even a trace of benzylidene acetal **50**. Only starting material was recovered. Using NH_4Cl as the quenching agent (in order to more closely reproduce Schreiber's conditions) was also unsuccessful. While we could have systematically varied the conditions of the reaction (base, temperature, time), we decided instead to examine two other related literature routes which, if successful, would allow us to make compounds similar to **50**.



40 **50** (X = SePh or H)

Scheme 14 - Our Attempts at the Schreiber Method

Several years ago, a comprehensive study was made by Bartlett on the stereoselective synthesis of 1,3-diol derivatives, starting from homoallylic alcohols.[19] This study is typified by the example shown in Scheme 15.

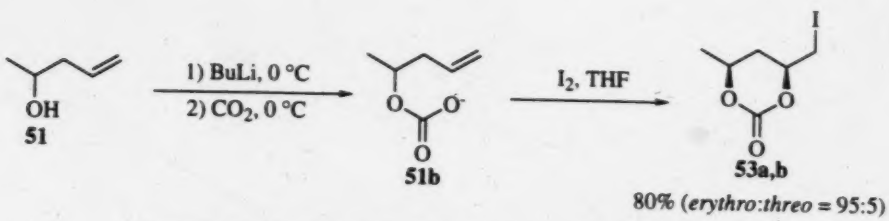


Scheme 15 - Bartlett Procedure for Forming 1,3-*syn*-diols

Conversion of the hydroxyl group of **51** into a *t*-butyl carbonate, followed by treatment with iodine at low temperature resulted in the formation of a mixture of 1,3-protected diols **53a,b**, with a preference for the *erythro* isomer. Numerous other examples were presented and, in most cases, the *erythro* (*syn*) isomer was the major product. The reaction was initiated by reversible formation of an iodonium ion (**52b**). Opening of the iodonium ion by the *t*-butyl carbonate produced a relatively stable carbonium ion **52c**, and the reaction was then completed by irreversible loss of a *t*-butyl cation to give carbonates **53a,b**.

Cardillo published closely related work (Scheme 16) in which many of the same examples were repeated, this time in a tandem sequence, without isolation of the initial alcohol derivative.[20] Thus, deprotonation of the hydroxyl group of **51** with BuLi, followed by addition of the alkoxide ion to carbon dioxide, gave intermediate **51b**. Upon activation of

the alkene by iodine, the carbonate cyclized to the same products (**53a,b**) as the Bartlett procedure, with a slightly different ratio of isomers.

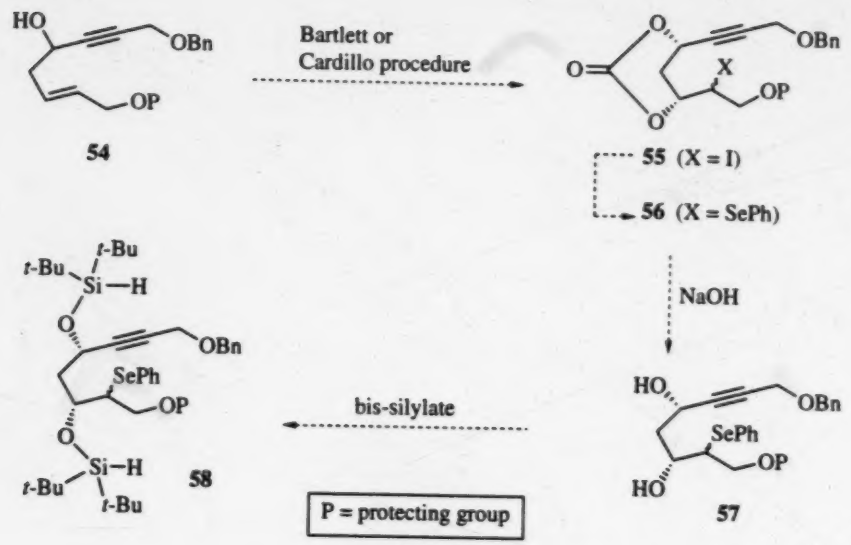


Scheme 16 - Cardillo Procedure for Forming 1,3-*syn*-diols

We felt that these related procedures would allow us to gain rapid access to a suitable radical cyclization substrate; our general plan is shown in Scheme 17. A compound of type **54** would be easily available from one of our earlier starting materials, and conversion into compound **56** could then be achieved by either the Bartlett or Cardillo procedures. Installation of a selenide could be effected either from iodide **55** or directly by activating the alkene with PhSeCl in place of iodine. A phenylselenide would be necessary in **56** for two principal reasons.

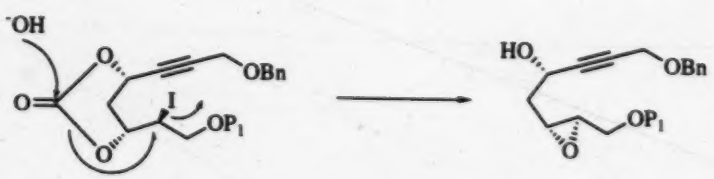
1) Removal of the carbonate protecting group under basic conditions leads to epoxidation in the presence of an adjacent halide (Scheme 18).[20]

2) The use of iodides as radical precursors is not suitable for our tandem cyclization, as demonstrated recently by Curran.[21] Halide transfer to the intermediate silicon radical would stop the tandem sequence from proceeding.



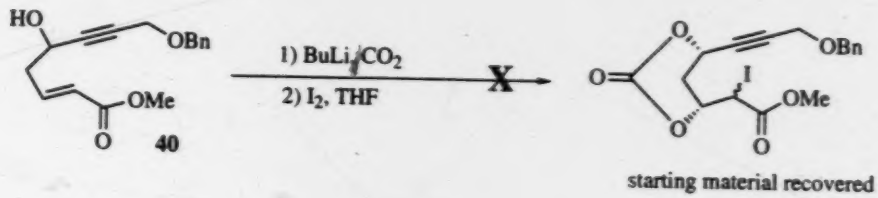
Scheme 17

We felt that, after removal of the carbonate, diol **57** could be bis-silylated (**57** → **58**). We were not sure if selective silylation could be accomplished on one of the hydroxyls of **57** (ideally, the silane would be installed preferentially on the C(9) alcohol). However, if we were forced to work with the bis-silane, we suspected that the C(11) silicon hydride would not interfere in the radical cyclization, as it is not suitably placed for hydrogen abstraction.



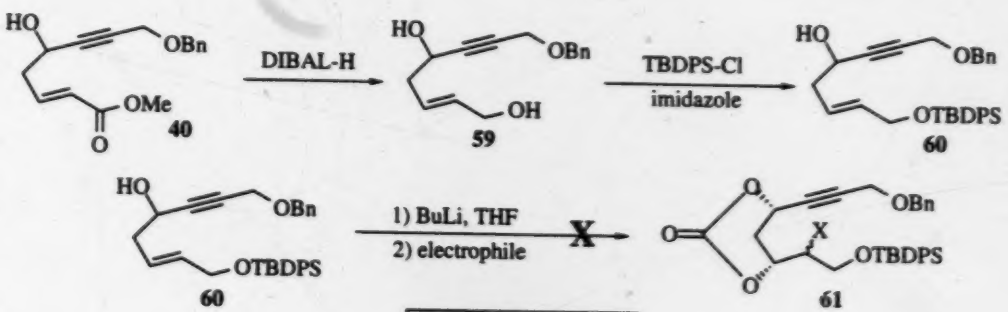
Scheme 18

Our initial attempt was a combination of the Cardillo and Schreiber methods (Scheme 19). Substrate **40** was a typical Schreiber-type substrate but we used Cardillo's conditions to try to form the *syn*-1,3-diol moiety.



Scheme 19

However, only starting material was recovered and so, in an attempt to more closely model the Cardillo substrates, we converted the α,β-unsaturated ester into a protected allylic alcohol (Scheme 20).

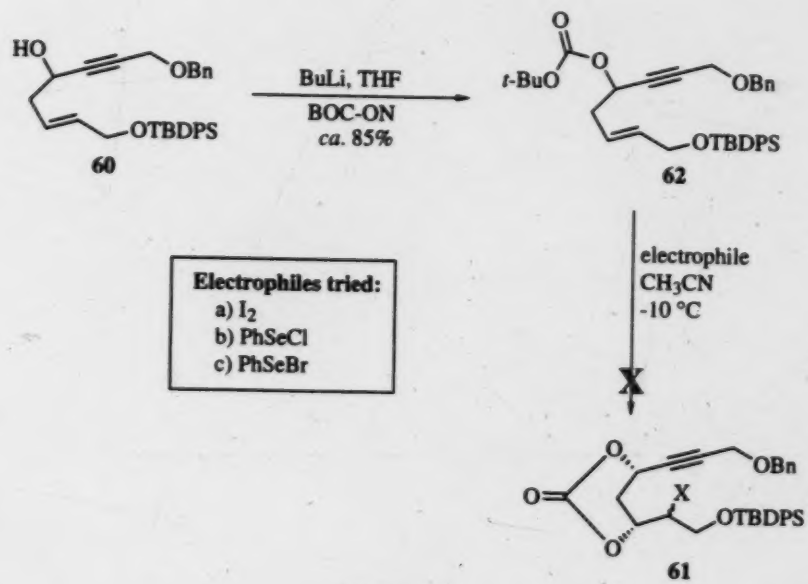


Electrophiles tried:

a) I_2
b) PhSeCl
c) PhSeBr
d) I_2, MCPBA
e) Br_2
f) PhSe-SePh

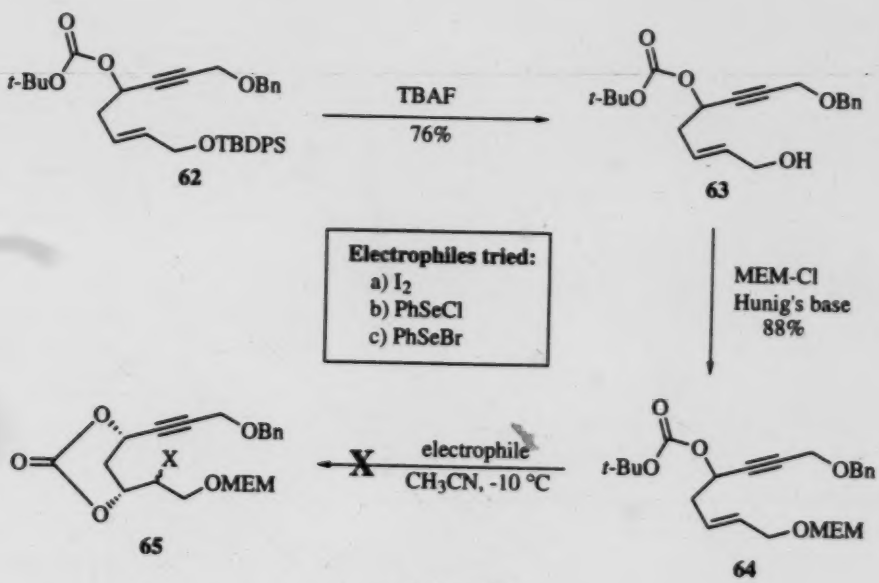
Scheme 20

This was accomplished by DIBAL reduction of **40** and selective protection of the primary alcohol of **59** (TBDPS-Cl). We then attempted to form *syn*-1,3-diols from compound **60** by using various electrophiles to activate the double bond (Scheme 20). Surprisingly, we obtained no trace of **61** under any conditions; the only compound ever isolated from the reaction mixtures was starting material. The lack of ring closure was very puzzling. Although the structure of our substrate **60** was different from the literature examples (*vide infra*), the basic feature of the homoallylic alcohol was the same. For completeness, we decided to attempt the reaction using the Bartlett conditions, which requires the formation and isolation of a *t*-butyl carbonate (Scheme 21).



Scheme 21

Therefore, we made carbonate **62**, but could not obtain it completely pure. Two extra peaks were observed in the ^1H NMR; they appeared to be due to the BOC-ON reagent. Nonetheless, we attempted the construction of the *syn*-1,3-diol **61**, but again observed no trace of the desired product. In some cases, starting material was isolated and in others, **60** was obtained (from loss of the *t*-butyl carbonate). In an attempt to obtain a pure carbonate of type **62**, we removed the TBDPS protecting group and replaced it with a MEM group (Scheme 22). Unlike compound **62**, carbonate **64** was obtained pure.



Scheme 22

This sequence also served to decrease the steric bulk around the alkene moiety, thus possibly making it more accessible to the electrophile. Under Bartlett's conditions,

however, we again failed to obtain a trace of 1,3-diol. It was obvious that we had exhausted our possibilities using this approach, but we did repeat one of the literature examples to ensure that our techniques and reagents were satisfactory, and obtained the compound that had been reported.

It was clear that our substrate was not suitable for this type of procedure. There were two features of our substrates which were potentially causing the failure of the reactions:

1) the presence of the alkyne adjacent to the homoallylic alcohol; no examples in the literature had this type of moiety,

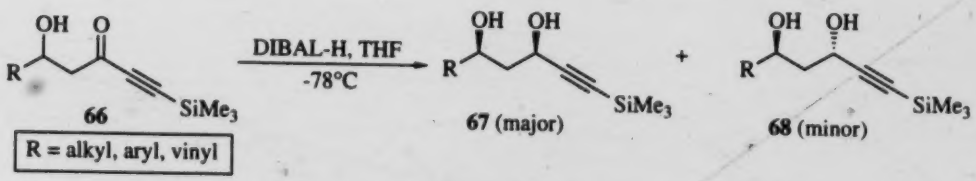
2) the oxygenated substituent on the double bond; most examples in the literature contained terminal olefins.

One potential idea to consider was to systematically vary our substrate to identify the structural feature that was incompatible. However, even if we did locate the problem, the efficiency of our method would be lost by removing any of the functional groups in our substrates, as they would have to be re-installed later. Therefore, we stopped work in this area, and adopted a new approach based on entirely different principles.

4.4 Formation of 1,3-diols by Stereoselective Reduction

Because of the surprising failure of the previous

methods to produce compounds with a *syn*-1,3-diol moiety, we were forced to search for other methods to accomplish the same goal. A literature search uncovered some work by Mohr on the stereoselective reduction of β-hydroxy acetylenic ketones.[22] The results can be summarized by the example shown in Scheme 23, in which diastereomeric 1,3-diols **67** and **68** were produced from the DIBAL-H reduction of **66**. The *syn*-1,3-diol **67** was the major product in this case and in most other examples; the ratio of *syn*:*anti* products ranged from 3:2 to 95:5.



Scheme 23 - Mohr Method of Making *syn*-1,3-diols

We recognized several aspects of this work which could be useful for our purposes.

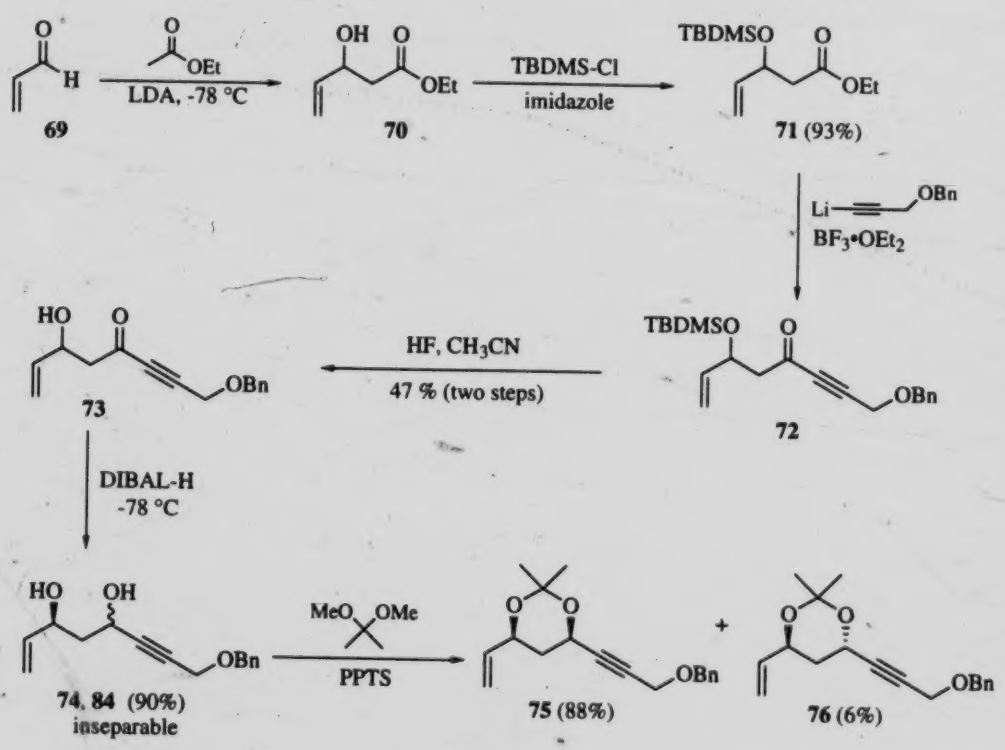
1) The major *syn*-1,3-diol produced in these reductions is the isomer needed for our synthesis.

2) The presence of an acetylene group adjacent to the 1,3-diol is ideal, as our required substrate contains this structural feature.

3) By making R a vinyl group, there exists a suitable handle for elaboration into an appropriate compound for the tandem radical cyclization.

The first two steps in this new approach (Scheme 24)

were literature procedures. Addition of ethyl lithioacetate to the carbonyl group of acrolein[23] resulted in formation of β-hydroxy ester **70**. Protection of the hydroxyl in the form of a silyl ether[24] then gave intermediate **71**. Conversion of **71** into an acetylenic ketone proceeded in moderate yield.

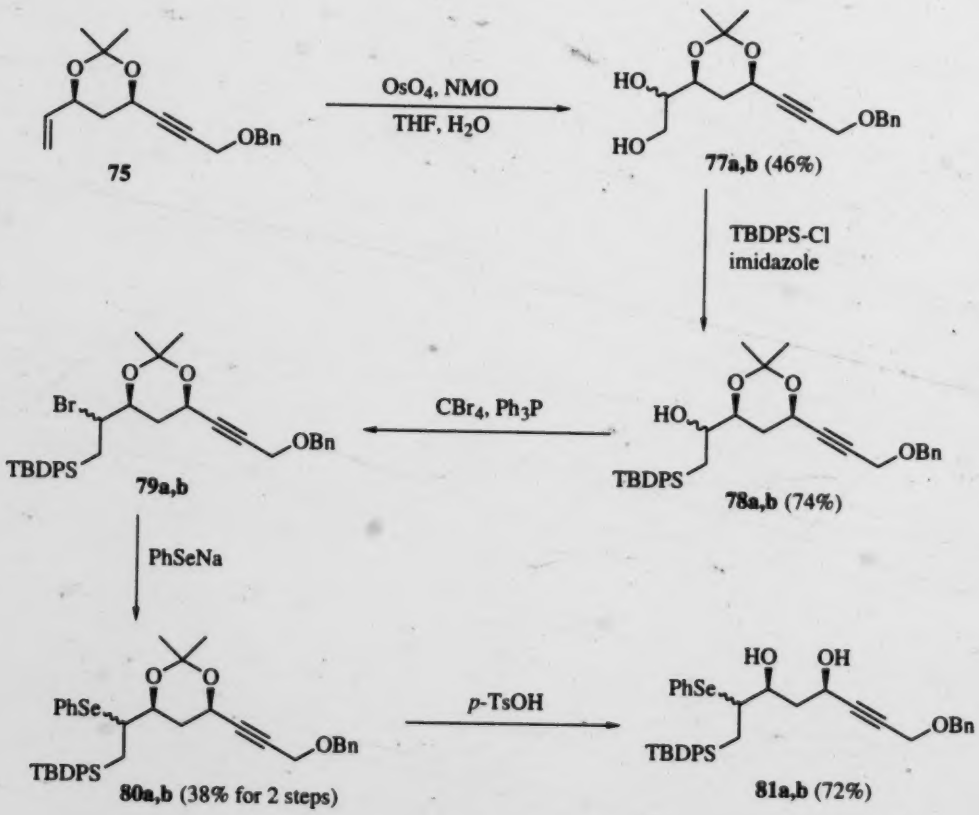


Scheme 24

The TBDMS ether was cleaved with HF[25] to regenerate the hydroxyl, in preparation for the reduction step to follow (the free hydroxyl is necessary for reduction to occur stereoselectively). DIBAL-H reduction then gave an inseparable mixture of 1,3-diols **74** and **84**. Protection of the 1,3-diols with an acetonide produced compounds **75** and **76**.

These materials were separated and it was found that the reduction step had proceeded with about 15:1 preference for the desired *syn* isomer.

Now that the unwanted acetonide **76** had been removed, the major isomer **75** could be carried forward. The vinyl group now had to be transformed by a number of steps into a form suitable for radical cyclization (Scheme 25). Conversion of the terminal olefin into diols **77a,b** proceeded in low yield.



Scheme 25

The formation of two compounds in this step was

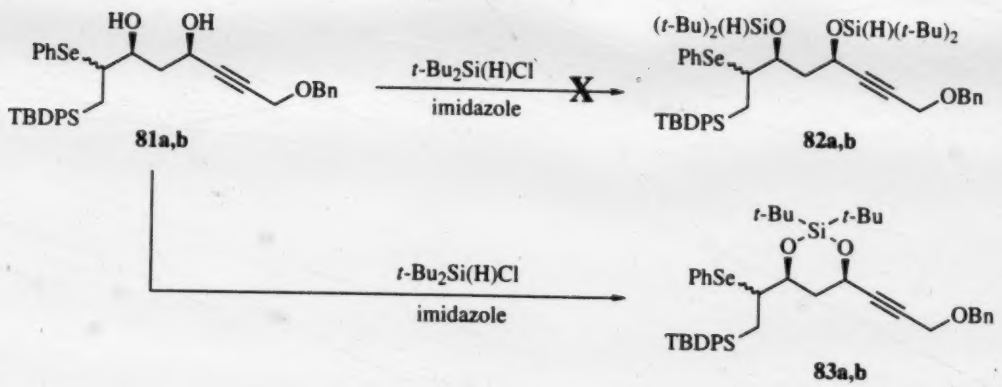
inconsequential as the initial stereochemistry at the secondary hydroxyl position would be destroyed later by formation of a radical. Selective protection of the primary alcohol as a TBDPS ether, followed by conversion of the remaining alcohol to a phenylselenide (via a two-step procedure), took us as far as compounds **80a,b**. Treatment of **80a,b** with acid then regenerated the 1,3-diol and we were seemingly one step away from our radical cyclization precursor.

The sole remaining transformation was that shown in Scheme 26 - attaching the silicon hydride to each of the hydroxyl groups in **81a,b**. As mentioned in the discussion of Section 4.3 (*vide supra*), we felt that a silicon hydride moiety on the C(11) hydroxyl would not interfere with the radical cyclization. The silylation proceeded only under vigorous conditions (overnight reflux) but we were finally able to isolate one new spot from the reaction mixture. However, upon examination of the ^{1}H NMR of this material, we quickly realized that **82a,b** had not been formed; we had instead probably isolated **83a,b**. These two unexpected isomers were not fully characterized but we assigned the structures based on the following ^{1}H NMR observations:

1) the signal for the di-*t*-butyl groups (*ca* δ 1 ppm) integrated for only 18 protons, not the expected 36,

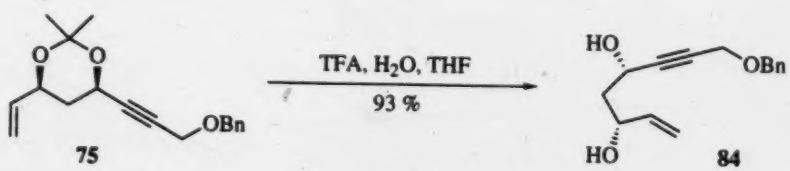
2) the hydroxyl protons were absent,

3) the Si-H signal, normally appearing at *ca* δ 4 ppm, was absent.



Scheme 26

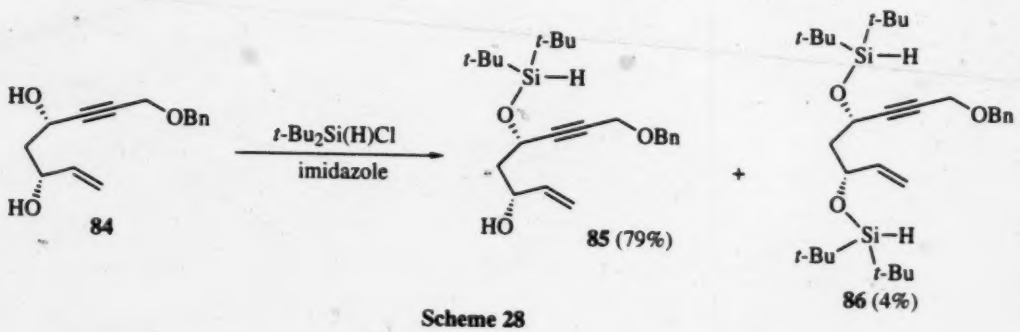
At this point, we felt that we had to alter, not our general approach, but the sequence in which the reactions were performed. To that end, the acetonide protecting group of **75** was removed (Scheme 27) to give *syn*-1,3-diol **84.** The immediate goal was to attach the silicon hydride moieties onto the hydroxyl groups in **84**. Following that step, we could elaborate the terminal alkene.



Scheme 27

The reaction involving the silicon hydride installations (Scheme 28) revealed two pleasant surprises. First, the reaction proceeded under very mild conditions (room temperature) compared to our previous attempt. It was not clear why, in this case, room temperature was suitable,

whereas vigorous heating was necessary for the related reaction of Scheme 26. Another key observation was that, upon examination of the reaction mixture by TLC, it was clear that one of the hydroxyls of **84** was being silylated at a much faster rate than the other. Decoupling experiments (see experimental section) indicated that the propargylic alcohol had been silylated preferentially; fortunately, the tandem radical reaction requires a silicon hydride on that particular hydroxyl.

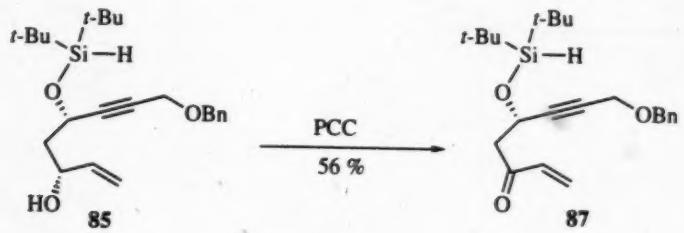


Scheme 28

Our speculation is that the propargylic alcohol is more sterically accessible due to the linear geometry of the adjacent alkyne. It was not possible to completely suppress formation of di-silylated compound **86**, but it was kept to a minimum after experimentation with the time of reaction and the quantity of silicon hydride used in the reaction. In any case, **86** could be desilylated (HF) and thus converted back to starting material **84**.

While awaiting the results of the decoupling

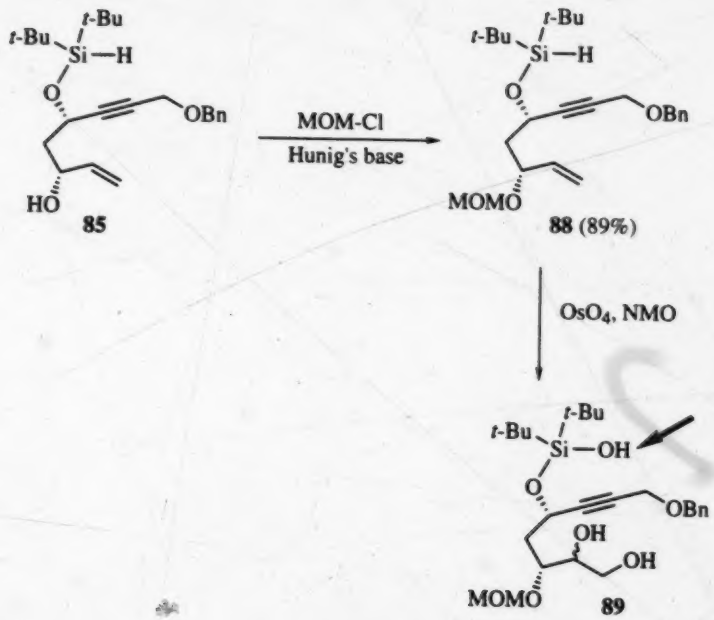
experiments, a chemical experiment was performed (Scheme 29) to confirm the structure of **85**. A small sample of **85** was treated with PCC and



Scheme 29

the resulting ketone **87** was characterized. The spectroscopic evidence indicated that **87** was a vinyl ketone (the olefinic protons of vinyl ketones are distinct in the ^{1}H NMR spectrum compared to standard double bonds), and thus demonstrated that the free hydroxyl in **85** was indeed positioned at C(11).

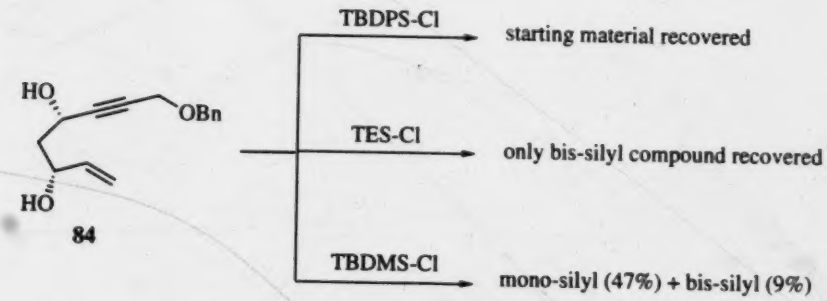
Compound **85** was further transformed (Scheme 30) by protecting the remaining allylic alcohol with a MOM group (**85** → **88**). We then attempted conversion of the terminal alkene of **88** into a diol by an OsO_4-mediated reaction. This transformation did indeed take place but was accompanied by conversion of the Si-H into a Si-OH moiety (**88** → **89**).[27] This unfortunate side reaction had also occurred in our earlier work (*vide supra*), when a silicon hydride was treated with *m*-CPBA.



Scheme 30

We could not proceed with this route due to the potential interference of the Si-OH group with subsequent reactions. It was evident that the silicon hydride would have to be introduced at a late stage in the synthesis (in any event, after the dihydroxylation). Thus, we were forced to go back to our original 1,3-diol **84** and attempt to selectively install a protecting group on the propargylic alcohol. We felt that for optimal selectivity, we required a protecting group of comparable steric bulk to the di-t-butyl silicon hydride. Initially, we attempted to introduce a TBDPS group (Scheme 31); however, TBDPS-Cl did not react easily with either hydroxyl, even under refluxing conditions. We then considered a less sterically demanding triethylsilyl moiety; however, even at low temperatures, selective

protection was impossible and both hydroxyl groups were protected.

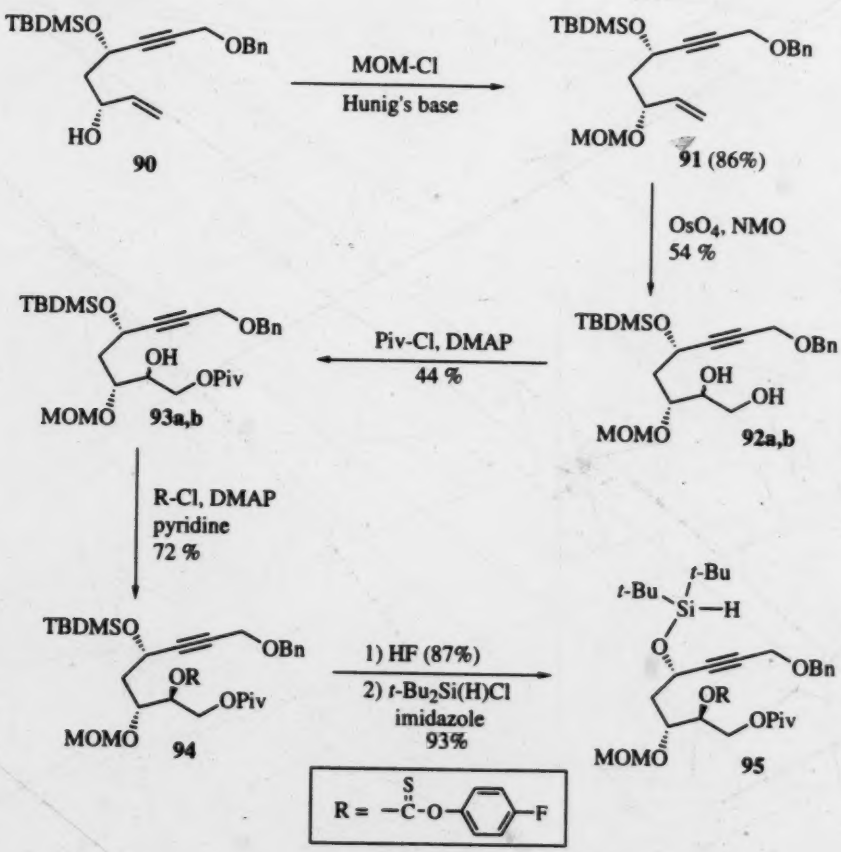


Scheme 31 - Attempts at Selective Protection

Finally, partial success was achieved by the use of a TBDMS group (see Scheme 31). Although not as selective for the propargylic alcohol as the di-*t*-butyl silicon hydride, the results were adequate for our purposes. The bis-silyl compound could be treated with HF and converted back to diol **84** (a significant amount of diol **84** is recovered in the reaction to begin with - see experimental section). By performing the reaction three times in this manner, we were able to build up a fairly large supply of the mono-silyl compound which allowed us to proceed with the synthesis. It is clear that the selective protection of the propargylic alcohol is highly sensitive to the bulk of the silicon reagent. In hindsight, a potentially useful protecting group would have been a di-*t*-butylmethylsilyl moiety. It would closely mimic the steric bulk of di-*t*-butylchlorosilane and in fact, might even be more selective in this example.

We proceeded using our previous experiments as a

guideline. The remaining hydroxyl group was protected with a MOM group (Scheme 32), and the stage was then set for elaboration of the double bond. Although diols **92a,b** were indeed produced, the yield was moderate. We spent a great deal of time trying to improve the yield but were unsuccessful.



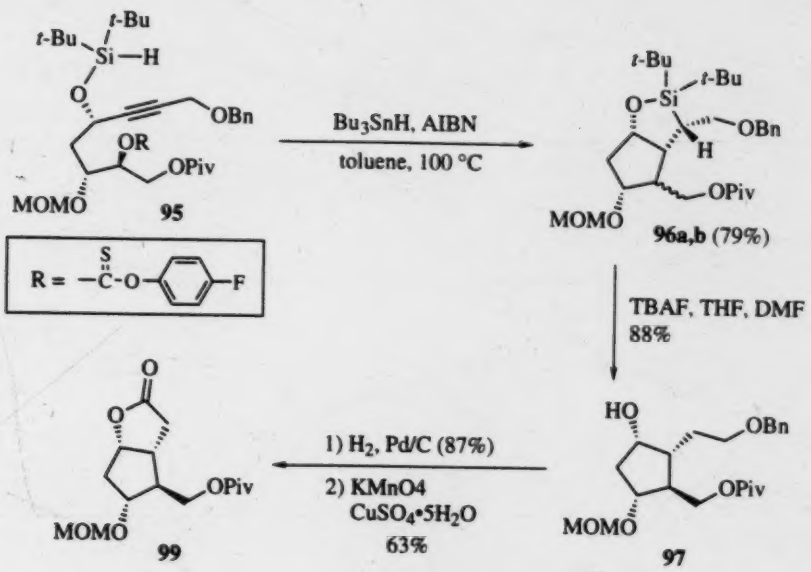
Scheme 32

Analysis of ^{13}C signal intensities indicated predominant formation of one of the isomers of **92a,b**, but this matter was not pursued. Selective protection of the primary hydroxyl

group in **92a,b** with a pivaloyl ester provided compounds **93a,b**. The very low yield in this step was extremely puzzling. We attempted the reaction by employing various conditions that had been reported previously,[28] but could not increase the yield significantly. The slow decomposition[29] of the mixture of diols **92a,b** forced us to accept the low yield in this step. Conversion of the remaining hydroxyl group into a suitable radical precursor met with some difficulty.

Attempts to convert that hydroxyl into a phenylselenide moiety by either a one or two step procedure[30] met with mixed results. The reactions were slow, as judged by TLC examination. We eventually decided to convert the hydroxyl into a Barton-type radical precursor (**93a,b** → **94**), and we also decided to proceed with the single diastereomer[31] **94** for several reasons. First of all, the relative R_f's of the two epimers was such that **94** was obtained pure while its epimer was slightly contaminated by an additional material (although upon re-chromatography, the epimer of **94** could be purified). Secondly, because the epimer of **94** is formed in relatively minor amounts, we would not be sacrificing a great deal of substrate by discarding it. Finally, the spectral analyses would be simplified with only one compound present.

The remaining two steps (before radical cyclization) were straightforward and proceeded smoothly. Thus, cleavage of the TBDMS ether, followed by introduction of the silicon hydride, afforded **95**, and we could now finally test our tandem radical cyclization on substrate **95**.



Scheme 33

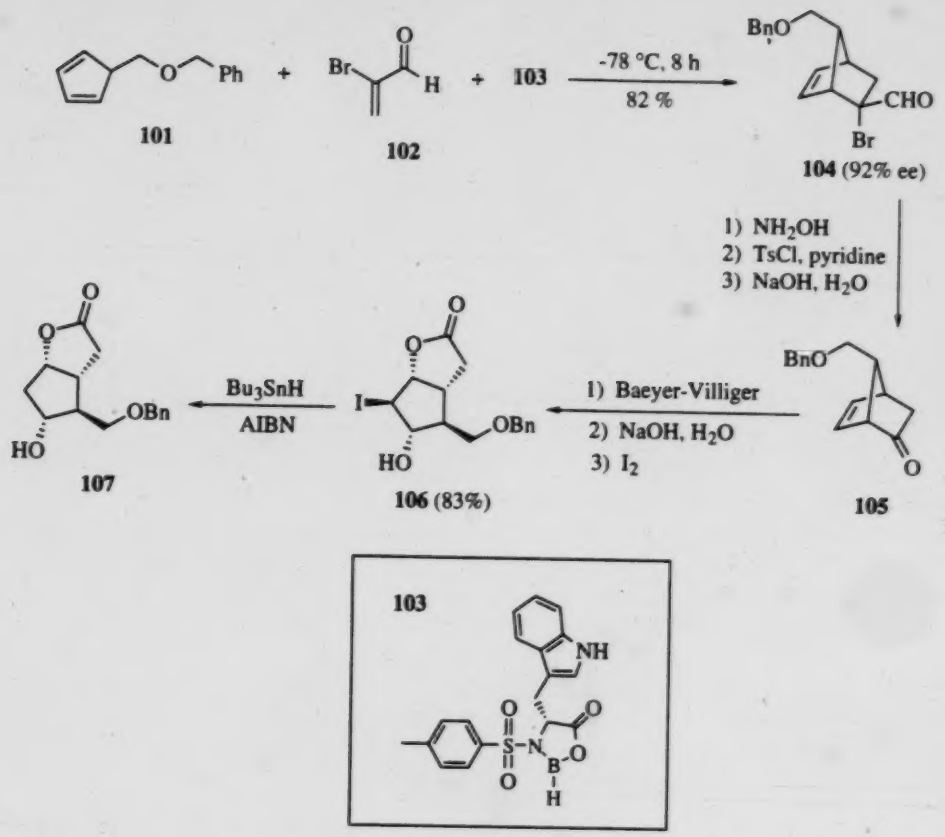
Treatment of **95** with Bu_3SnH in toluene (reflux), using AIBN as the radical initiator (Scheme 33), gave a mixture of bicyclic compounds **96a,b**. The compounds could not be separated at this stage, although there were no tin residues remaining, which was very helpful. Conversion of this mixture into a Corey lactone derivative followed the same path as was used for the 11-deoxy Corey lactone. Cleavage of the silicon-containing ring by the Stork procedure (TBAF, DMF, 70 °C) gave alcohol **97** as a single diastereomer. The minor diastereomer could be separated at this stage and was discarded. Hydrogenolysis of the benzyl group (H_2, Pd/C) gave diol **98**, and the sequence was completed by a one step lactonization to produce compound **99**, which is a protected form of the Corey lactone.

5. Conclusions

In this study, we have demonstrated the ability to form highly substituted cyclopentane rings in a stereoselective manner by utilizing a tandem radical cyclization reaction. The compounds we synthesized are bicyclic lactones which are commonly used as intermediates in prostaglandin synthesis. Specifically, we have introduced a new synthesis of the Corey lactone. While our route to this important prostaglandin intermediate is lengthy (18 steps), it still compares favourably with many prior syntheses.[32]

However, the elegant routes introduced by Corey and Stork remain the standards in this area. Both routes are efficient (eight steps), high-yielding, and result in the formation of an enantiomerically pure compound.

Corey's work[33] began with a catalytic enantioselective Diels-Alder reaction (Scheme 34) to give intermediate **104** in high enantiomeric excess. A sequence of oxime formation and bromide solvolysis, tosylation and elimination to the cyanohydrin, and basic hydrolysis led to **105**. Baeyer-Villiger reaction, followed by hydrolysis of the intermediate lactone, and an iodolactonization reaction, then produced advanced intermediate **106**. Finally, reduction of the iodide gave the Corey lactone derivative **107**.

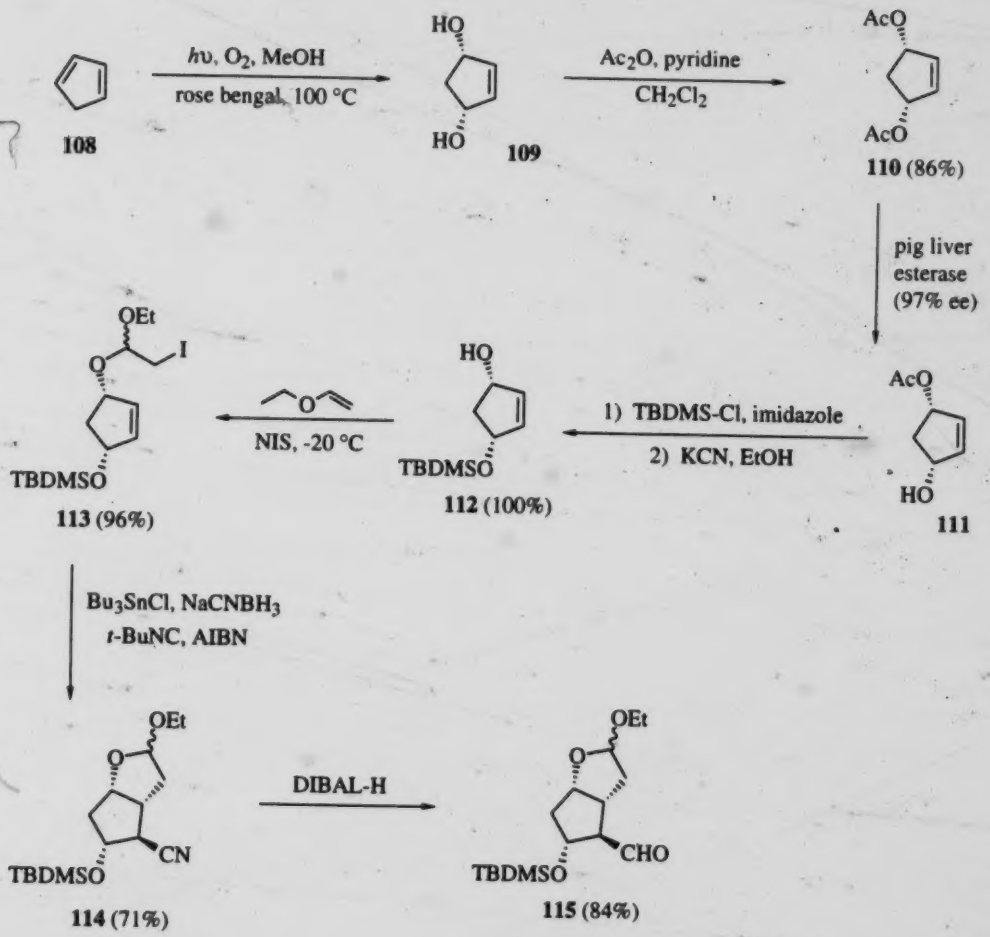


101 102 104 (92% ee) 105 106 (83%) 107

Scheme 34

In the Stork synthesis (Scheme 35),[34] a photooxygenation and reduction sequence, involving cyclopentadiene, produced *meso*-diol **109**. Conversion to the *meso*-diacetate then allowed enzymatic transformation to the monoacetate **111**, in high enantiomeric excess. Protecting group manipulation then gave **112**, which was converted to the mixed iodoacetal **113**, upon treatment with ethyl vinyl ether and NIS. Radical cyclization, followed by radical trapping with *tert*-butyl isocyanide, afforded **114**, and DIBAL-H reduction then gave

aldehyde **115**. While not a lactone, **115** is closely related to the Corey lactone class of intermediates.



Scheme 35

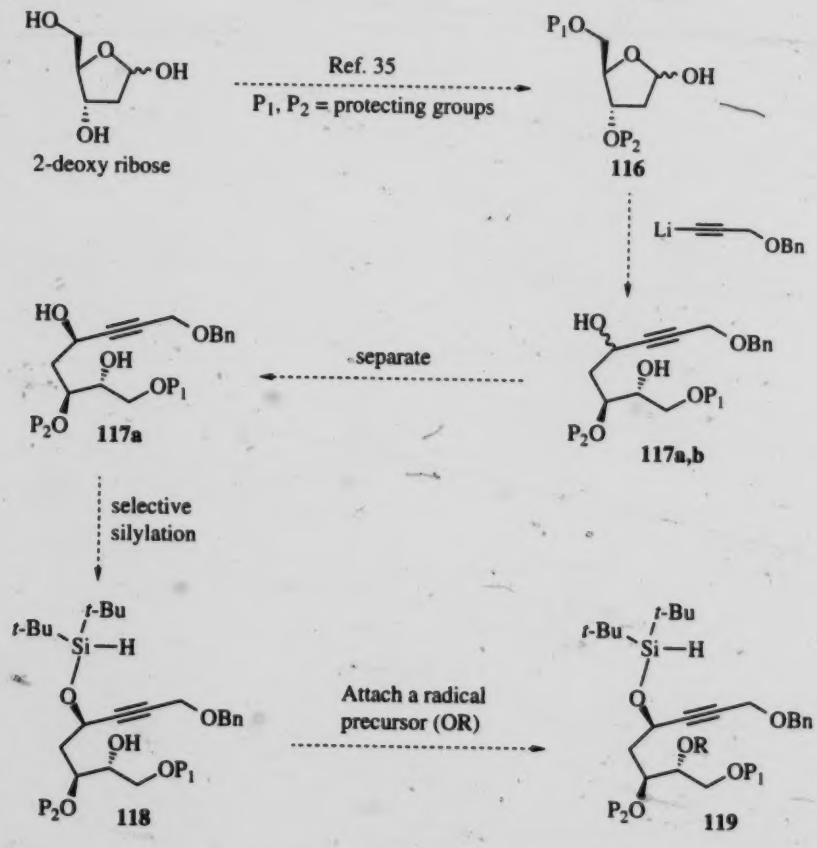
Our synthesis does not match the efficiency of the above methods, but the final four step sequence (starting with the tandem radical cyclization - Scheme 33) results in the conversion of an acyclic compound into the Corey lactone,

with good stereoselectivity. The yields are also reasonably high. A more concise synthesis of an appropriate radical cyclization precursor would be desirable, and the potential exists to improve our synthesis of the Corey lactone-type substrates. Scheme 36 shows an alternate approach. In this strategy, the starting material is 2-deoxy ribose, a relatively inexpensive and commercially available material. Known procedures[35] would allow the protection of the two indicated hydroxyls (formation of a methyl glycoside and subsequent removal would temporarily block the lactol). Compound **116** should easily be convertible into diastereomers **117a,b**. It is doubtful that any stereoselectivity would be observed in this step. If **117a** and **117b** are separable, the correct isomer (**117a**) could then be silylated preferentially at the propargylic alcohol (we have observed in our earlier studies that this discrimination was indeed possible). Installation of a radical precursor (probably the Barton-type moiety that we used earlier) would then give compound **119**, which could undergo the tandem radical cyclization reaction. The cyclization and subsequent steps would take place analogously to our earlier synthesis.

This new approach may be superior for several reasons:
1) by starting with an enantiomerically pure carbohydrate, we would obtain the optically active Corey lactone, although, in the case of 2-deoxy-*D*-ribose, the unnatural stereochemistry will be obtained,
2) the sequence leading to the radical cyclization precursor

is much shorter than our earlier sequence,

3) all oxygen functionality we require is present from the start - this would enable us to avoid the OsO_4-mediated dihydroxylation, which had earlier caused the Si-H unit to be transformed.



Scheme 36

This approach is currently under investigation in these laboratories.

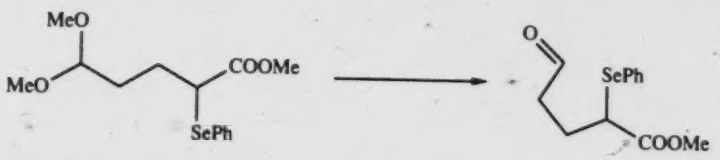
EXPERIMENTAL

Methyl 5,5-Dimethoxy-2-(phenylseleno)pentanoate (13).

12 **13**

n-BuLi (2.5 M in hexanes, 6.29 mL, 15.73 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of freshly distilled *N*-isopropylcyclohexylamine (2.59 mL, 15.73 mmol) in dry THF (8 mL). After 15 min, methyl (phenylseleno)acetate (3.27 g, 14.30 mmol) in dry THF (4 mL plus 2 mL as a rinse) was added dropwise at -78 °C. After 30 min, the cold bath was removed and the solution was allowed to warm to room temperature (over *ca.* 40 min). The enolate solution was added quickly (*ca.* 2 min) to a room temperature solution of 1,1-dimethoxy-3-iodopropane (4.93 g, 21.44 mmol) in dry DMSO (20 mL), and stirring was continued for 3 h. Water (200 mL) was added and the aqueous solution was extracted with EtOAc until extraction was complete (TLC control, silica, 1:4 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. The crude product was used in the next step without characterization.

Methyl 5-Formyl-2-(phenylseleno)pentanoate (14).



13 **14**

An aqueous solution of TFA (50%, 30 mL) was added dropwise to a stirred solution of **13** (crude material from previous reaction) in CH_2Cl_2 (70 mL) and the resulting heterogeneous mixture was stirred vigorously for 14 h at room temperature. The mixture was cooled (0 °C) and titrated with saturated aqueous $NaHCO_3$ until basic (pH paper). The aqueous solution was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 1:4 EtOAc-hexane). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.5 × 28 cm), using 15:85 EtOAc-hexane, gave aldehyde **14** (2.152 g, 53% over two steps) as a pure (^1H NMR, 200 MHz), pale yellow oil: FTIR (CH_2Cl_2 cast) 1728 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.95-2.20 (m, 2 H), 2.60 (dt, J = 7.3, 1.2 Hz, 2 H), 3.55-3.70 (m, 4 H), 7.25-7.40 (m, 3 H), 7.52-7.65 (m, 2 H), 9.71 (t, J = 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.2 (t'), 42.0 (t'), 42.4 (d'), 52.2 (q'), 127.3 (s'), 128.8 (d'), 129.2 (d'), 135.8 (d'), 172.9 (s'), 200.6 (d'); exact mass m/z calcd for $C_{12}H_{14}O_3Se$ 286.0108, found 286.0100. Anal. Calcd for $C_{12}H_{14}O_3Se$: C, 50.54; H, 4.95. Found: C, 50.57; H, 4.95.

Methyl (2*R,5*R**)- and (2*R**,5*S**)-5-Hydroxy-8-phenylmethoxy-2-(phenylseleno)-6-octynoate (15).**

14 **15**

n-BuLi (2.5 M in hexanes, 6.42 mL, 16.0 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of benzyl propargyl ether (2.340 g, 16.04 mmol) in dry THF (50 mL). After 15 min, aldehyde **14** (2.286 g, 8.02 mmol) in dry THF (10 mL plus 5 mL as a rinse) was added dropwise at -78 °C. After 2 h, the cold solution was poured slowly into water (200 mL), and extracted with EtOAc until extraction was complete (TLC control, silica, 1:3 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.5 × 24 cm), using 1:3 EtOAc-hexane, gave alcohol **15** (2.676 g, 77%) as a pure (^1H NMR, 200 MHz), pale yellow oil: FTIR (CH_2Cl_2 cast) 1728, 3435 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.61-2.20 (m, 5 H), 3.55-3.75 (m, 4 H), 4.20 (s, 2 H), 4.32-4.50 (m, 1 H), 4.55 (s, 2 H), 7.21-7.45 (m, 8 H), 7.51-7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.4 (t'), 35.7 (t'), 42.9 (d'), 52.0 (q'), 57.3 (t'), 61.6 (d'), 71.6 (t'), 81.0 (s'), 87.0 (s'), 127.5 (s'), 127.8 (d'), 128.0 (d'), 128.4 (d'), 128.6 (d'), 129.0 (d'), 135.7 (d'), 137.2 (s'), 173.2

(s') (We assume coincident peaks). Anal. Calcd for $C_{22}H_{23}O_4Se$: C, 61.25; H, 5.61. Found: C, 61.42; H, 5.47.

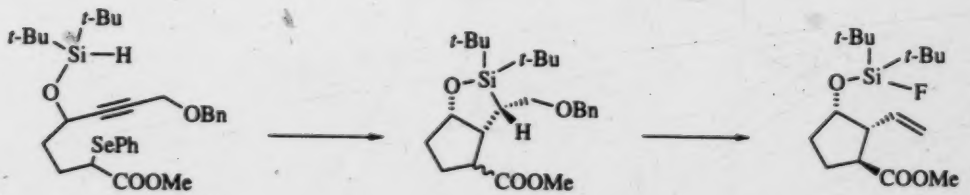
Methyl (2*R,5*S**)- and (2*R**,5*R**)-5-[[Bis(1,1-dimethyl)-ethylsilyl]oxy]-8-(phenylmethoxy)-2-(phenylseleno)-6-octynoate (10).**

15 **10**

Imidazole (860.3 mg, 12.64 mmol) and *t*-Bu_2SiHCl (1.60 mL, 7.90 mmol) were added consecutively to a stirred solution of alcohol **15** (2.723 g, 6.32 mmol) in dry THF (50 mL). The resulting white suspension was stirred and refluxed for 12 h. The mixture was allowed to cool to room temperature and was then poured into water (100 mL). The aqueous mixture was extracted with EtOAc until extraction was complete (TLC control, silica, 5:95 EtOAc-hexane), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 22 cm), using 5:95 EtOAc-hexane, gave **10** as an inseparable mixture (^{13}C NMR) of diastereomers (3.428 g, 95%). The material was a colorless oil: FTIR (CH_2Cl_2 cast) 1733, 2094 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 0.85-1.10 (m, 18 H), 1.67-2.21 (m, 4 H), 3.50-3.75 (m, 4 H), 4.10 (s, 1 H), 4.12-

4.22 (m, 2 H), 4.48-4.62 (m, 3 H), 7.20-7.42 (m, 8 H), 7.52-7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.7 (s'), 20.0 (s'), 27.2 (q'), 27.4 (t'), 36.4 (t'), 36.5 (t'), 43.1 (d'), 43.2 (d'), 51.9 (q'), 57.2 (t'), 65.6 (d'), 71.3 (t'), 81.1 (s'), 81.2 (s'), 86.8 (s'), 127.6 (s'), 127.8 (d'), 128.1 (d'), 128.4 (d'), 128.5 (d'), 129.0 (d'), 135.6 (d'), 135.7 (d'), 137.5 (s'), 173.1 (s') (We assume coincident peaks); exact mass *m/z* calcd for $C_{30}H_{42}O_4SeSi$ 574.2018, found 574.2020. Anal. Calcd for $C_{30}H_{42}O_4SeSi$: C, 62.81; H, 7.38. Found: C, 62.98; H, 7.42.

Methyl-(1α,2β,3β)-(±)-3-[[[Bis(1,1-dimethylethyl] fluoro-silyl]oxy]-2-(ethenyl)cyclopentanecarboxylate (17).



10 **16a,b** **17**

A solution of Ph_3SnH (1.00 g, 2.85 mmol) and AIBN (40.7 mg, 0.25 mmol) in dry PhH (20 mL) was added over 6 h (syringe pump) to a refluxing solution of **10** (1.421 g, 2.48 mmol) in dry PhH (120 mL). Refluxing was continued for 2 h after the addition. The mixture was cooled to room temperature, and evaporated. Flash chromatography of the residue over silica gel (3 × 21 cm), using 5:95 EtOAc-hexane, gave **16a,b**,

contaminated with tin residues. Esters **16a,b** were not purified further but used directly in the next step. Boron trifluoride etherate (1.47 mL, 12.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **16a,b** (from the previous reaction) in dry CH_2Cl_2 (25 mL). The cold bath was removed and the solution was stirred for an additional 14 h, at which time water (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 3:7 CH_2Cl_2-hexane). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 19 cm), using 3:7 CH_2Cl_2-hexane, gave **17** (409.0 mg, 50% for two steps) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$ cast) 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.0 (s, 9 H), 1.04 (s, 9 H), 1.79-2.03 (m, 3 H), 2.09-2.27 (m, 1 H), 2.60-2.73 (m, 1 H), 2.84-2.99 (m, 1 H), 3.67 (s, 3 H), 4.51-4.61 (m, 1 H), 5.0-5.14 (m, 2 H), 5.81-5.99 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.7 (s'), 20.0 (s'), 20.4 (s'), 20.7 (s'), 26.9 (q'), 27.0 (t'), 27.1 (q'), 34.7 (t'), 46.7 (d'), 51.5 (d'), 54.9 (q'), 79.0 (d'), 116.7 (t'), 136.4 (d'), 176.4 (s') (the two extra signals at δ20.0 and δ 20.7 are due to ^{19}F coupling); exact mass *m/z* calcd for $C_{16}H_{28}O_2SiF$ (M-OCH_3) 299.1843, found 299.1840.

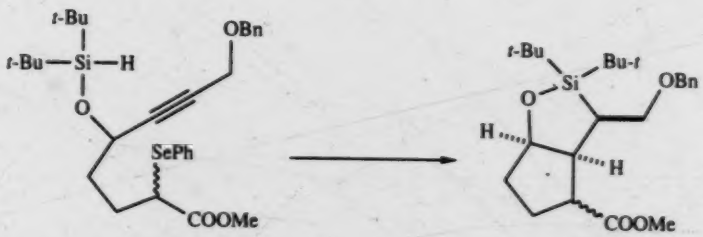
(1α,2β,3β)-(±)-3-[[[Bis(1,1-dimethylethyl]fluorosilyl]-oxy]-2-(ethenyl)cyclopentanemethanol (18).

17 **18**

A solution of **17** (280.2 mg, 0.85 mmol) in dry THF (6 mL) was added dropwise to a stirred and cooled (-78 °C) slurry of $LiAlH_4$ (32.2 mg, 0.85 mmol) in dry THF (20 mL). The cold bath was removed and the mixture was allowed to reach room temperature (*ca.* 30 min). The mixture was then cooled to 0 °C, at which time water (20 mL) was added. The aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 1:4 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 1:4 EtOAc-hexane, gave **18** (240.2 mg, 94%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3335 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0 (s, 9 H), 1.04 (s, 9 H), 1.71-2.42 (m, 6 H), 3.45-3.77 (m, 3 H), 4.48-4.59 (m, 1 H), 5.0-5.15 (m, 2 H), 5.86-6.10 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.8 (s'), 20.1 (s'), 20.5 (s'), 20.8 (s'), 25.7 (t'), 26.9 (q'), 27.1 (q'), 34.5 (t'), 44.0 (d'), 53.8 (d'), 65.8 (t'), 79.4 (d'), 116.2 (t'), 138.8 (d') (the two extra signals at δ 20.1 and δ 20.8 are due to ^{19}F coupling); exact mass *m/z* calcd for $C_{12}H_{22}O_2FSi$ ($M-C_4H_9$)

245.1373, found 245.1372.

Methyl (3α,3aβ,4α,6aβ)- and (3α,3aβ,4β,6aβ)-(±)-2,2-Bis-(1,1-dimethylethyl)hexahydro-3-[(phenylmethoxy) methyl]-2*H*-cyclopent[*d*]-[1,2]oxasilole-4-carboxylate (16a,b).



10 **16a,b**

A solution of Ph_3SnH (629.0 mg, 1.79 mol) and AIBN (33.9 mg, 0.21 mmol) in dry PhH (20 mL) was added over 7 h by syringe pump to a refluxing solution of **10** (790.0 mg, 1.38 mmol) in dry PhH (100 mL). Refluxing was continued for 1 h after the addition, and the mixture was then allowed to cool to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (4 × 20 cm), using 5:95 EtOAc-hexane, gave crude **16a,b**, contaminated with tin residues. It was used directly in the next step, without full characterization.

(3α,3aβ,4α,6aβ)- and (3α,3aβ,4β,6aβ)-(±)-2,2-Bis(1,1-dimethylethyl)hexahydro-3-[(phenylmethoxy)methyl]-2*H*-cyclopent[*d*]-[1,2]oxasilol-4-yl]methanol (22).

16a,b **22**

A solution of crude **16a,b** (from the previous reaction) in dry THF (5 mL plus 2 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) suspension of $LiAlH_4$ (52.31 mg, 1.38 mmol) in dry THF (20 mL). After 5 min, the resulting mixture was allowed to cool to room temperature and was then poured into ice water (50 mL). The aqueous solution was extracted with EtOAc until extraction was complete (TLC control, silica, 1:4 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 21 cm), using 1:4 EtOAc-hexane, gave alcohol **22**, which was contaminated (^1H NMR) with some impurities that were not separable by flash chromatography. Alcohol **22** was used in the next step without full characterization. We depict **22** arbitrarily as a mixture of isomers, but we do not know for a fact whether one of the impurities is the isomer, or a totally different compound.

(1α,2α,3β)-(±)-3-Hydroxymethyl-2-[2-[2-(phenylmethoxy)-ethyl]ethyl]cyclopentanol (23).

22 **23**

TBAF (1.0 M in THF, 30 mL, 30 mmol) was added dropwise to a stirred solution of impure alcohol **22** in DMF (25 mL). The resulting solution was heated at 60 °C for 3 h, cooled to room temperature, and poured into water (100 mL). The mixture was extracted with EtOAc until extraction was complete (TLC control, silica, 3:1 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 18 cm), using 3:1 EtOAc-hexane, gave diol **23**, which was contaminated (^1H NMR) with some impurities that were not separable by flash chromatography. Diol **23** was used in the next step without full characterization. We arbitrarily depict **23** as a single isomer, but we do not know if the isomer of **23** is one of the impurities.

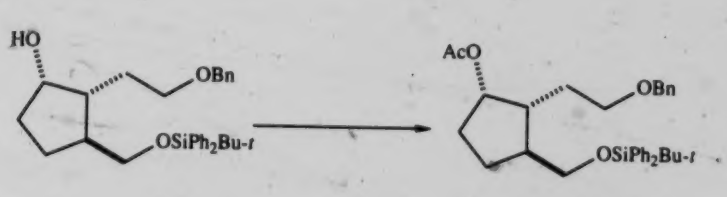
(1α,2α,3β)-(±)-3-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]-methyl]-2-[2-(Phenylmethoxy)ethyl]cyclopentanol (24).

23 **24**

Imidazole (96.7 mg, 1.42 mmol) and *t*-$BuPh_2SiCl$ (0.259 mL, 0.995 mmol) were added successively to a room temperature solution of impure diol **23** (obtained from the previous reaction) in dry CH_2Cl_2 (20 mL). After 1 h, water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 15:85 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 20 cm), using 15:85 EtOAc-hexane, gave alcohol **24** (222.8 mg, 33% over four steps) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3450 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.05 (s, 9 H), 1.40-2.08 (m, 8 H), 2.68 (s, 1 H), 3.32-3.73 (m, 4 H) 4.23 (s, 1 H), 4.48 (s, 2 H), 7.21-7.50 (m, 11 H), 7.58-7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.3 (s'), 26.3 (t'), 26.9 (q'), 28.8 (t'), 33.0 (t'), 45.1 (d'), 47.6 (d'), 66.4 (t'), 70.5 (t'), 73.5 (t'), 74.6 (d'), 127.6 (d'), 127.7 (d'), 128.5 (d'), 129.6 (d'), 134.0 (s'), 135.7 (d'), 137.9 (s') (We assume a coincident peak in the aromatic region). Anal.

Calcd for $C_{31}H_{40}O_3Si$: C, 76.18; H, 8.25. Found: C, 76.28; H, 8.29.

(1α,2α,3β)-(±)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-methyl]-2-[[2-(phenylmethoxy)]ethyl]cyclopent-1-yl Acetate (25).



24 **25**

Et_3N (0.074 mL, 0.530 mmol), Ac_2O (0.067 mL, 0.706 mmol), and DMAP (8.6 mg, 0.071 mmol) were added consecutively to a stirred solution of alcohol **24** (172.3 mg, 0.353 mmol) in dry CH_2Cl_2 (15 mL). After 2 h, saturated aqueous NH_4Cl (25 mL) was added, and the mixture was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 21 cm), using 1:9 EtOAc-hexane, gave **25** (182.0 mg, 97%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (neat film) 1735 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.05 (s, 9 H), 1.55-2.15 (m, 11 H), 3.30-3.50 (m, 2 H), 3.58 (dd, J = 10.1, 5.5 Hz, 1 H), 3.70 (dd, J = 10.1, 4.4 Hz, 1 H), 4.40 (s, 2 H), 5.12-5.23 (m, 1 H), 7.20-7.50 (m, 11 H), 7.59-7.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.2 (s'), 21.2 (q'), 25.9 (t'), 26.8 (q'), 28.4 (t'), 31.6

(t'), 42.3 (d'), 45.0 (d'), 66.0 (t'), 69.0 (t'), 72.8 (t'), 77.9 (d'), 127.4 (d'), 127.6 (d'), 128.3 (d'), 129.5 (d'), 133.7 (s'), 135.6 (d'), 138.5 (s'), 170.6 (s') (We assume a coincident peak). Anal. Calcd for $C_{33}H_{42}O_4Si$: C, 74.68; H, 7.98. Found: C, 74.69; H, 7.95.

(1α,2α,3β)-(±)-2-[[2-Hydroxyethyl]-3-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]methyl]cyclopent-1-yl Acetate (26).

25 **26**

Pd/C (10%, 43.7 mg) was added to a solution of **25** (437.6 mg, 0.824 mmol) in bench MeOH (15 mL). The mixture was stirred under a H_2 atmosphere (balloon) for 20 h, filtered through a short pad (0.5 × 2 cm) of Celite, and evaporated. Flash chromatography of the residue over silica gel (1 × 18 cm), using 3:7 EtOAc-hexane, gave alcohol **26** (333.8 mg, 92%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1735, 3447 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 1.05 (s, 9 H), 1.40-2.15 (m, 12 H), 3.42-3.78 (m, 4 H), 5.13-5.28 (m, 1 H), 7.29-7.50 (m, 6 H), 7.55-7.79 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.2 (s'), 21.2 (q'), 25.7 (t'), 26.8 (q'), 31.1 (t'), 31.5 (t'), 42.4 (d'), 44.8 (d'), 61.7 (t'), 66.1 (t'), 78.2 (d'), 127.6 (d'), 129.6 (d'), 133.6 (s'), 135.6 (d'),

170.9 (s'); exact mass *m/z* calcd for $C_{22}H_{27}O_4Si$ ($M-C_4H_9$) 383.1679, found 383.1672. Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.23. Found: C, 70.76; H, 8.55.

(1α,2α,3β)-(±)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]-oxy]methyl]-2-(2-oxoethyl)cyclopent-1-yl Acetate (27).

26 **27**

Alcohol **26** (119.6 mg, 0.272 mmol) in dry CH_2Cl_2 (3 mL plus 1 mL as a rinse) was added dropwise to a stirred mixture of PCC (76.1 mg, 0.353 mmol) and molecular sieves (4 Å, 25.4 mg) in dry CH_2Cl_2 (5 mL). After 2.5 h, the mixture was filtered through a short pad (0.5 × 1 cm) of silica gel, using 2:3 EtOAc-hexane to elute the desired compound. Evaporation of the filtrate, and flash chromatography of the residue over silica gel (1 × 16 cm), using 15:85 EtOAc-hexane, gave aldehyde **27** (110.4 mg, 93%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1737 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.05 (s, 9 H), 1.43-1.62 (m, 1 H), 1.62-1.79 (m, 1 H), 1.81-2.13 (m, 6 H), 2.28-2.64 (m, 3 H), 3.57-3.72 (m, 2 H), 5.16-5.29 (m, 1 H), 7.30-7.50 (m, 6 H), 7.55-7.75 (m, 4 H), 9.69 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.2 (s'), 21.1 (q'), 25.5 (t'), 26.8 (q'), 31.4 (t'), 39.9 (d'), 43.1 (t'), 44.7 (d'), 65.8 (t'), 77.7 (d'), 127.7

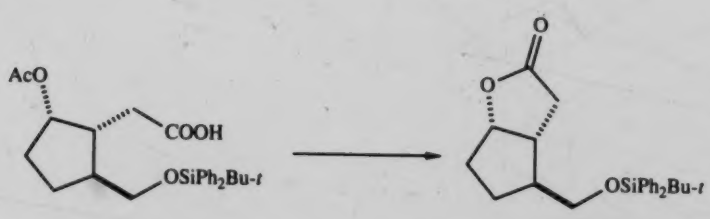
(d'), 129.7 (d'), 133.4 (s'), 135.5 (d'), 170.4 (s'), 201.3 (d'). Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.14; H, 7.82.

(1α,2α,5β)-(±)-2-Acetyloxy-5-[[[(1,1-dimethylethyl)-diphenylsilyl]oxy]methyl]cyclopentaneacetic Acid (28).

27 **28**

A solution of $NaClO_2$ (228 mg, 2.52 mmol) and Na_2HPO_4 (212 mg, 1.76 mmol) in *t*-BuOH (10 mL) was added dropwise to a stirred and cooled (0 °C) solution of aldehyde **27** (110.4 mg, 0.252 mmol) and 2-methyl-2-butene (1.34 mL, 12.6 mmol) in *t*-BuOH (20 mL). After 2 h, the cold-bath was removed and stirring was continued for an additional 24 h. The solution was poured into saturated aqueous NH_4Cl (25 mL) and the aqueous solution was extracted with EtOAc until extraction was complete (TLC control, silica, EtOAc). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 17 cm), using EtOAc, gave carboxylic acid **28** as an impure (^1H NMR) oil. The compound was not characterized, but used directly in the next step.

(3aα,4β,6aα)-(±)-4-[[[(1,1-Dimethylethyl)diphenyl silyl]-oxy]methyl]hexahydrocyclopenta[*b*]furan-2-one (31).

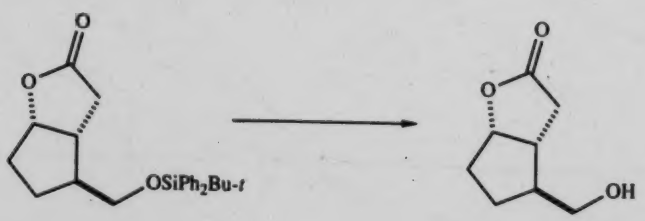


28 **31**

K_2CO_3 (104.5 mg, 0.756 mmol) was added to a solution of carboxylic acid **28** (obtained from the previous reaction) in MeOH (10 mL). The solution was refluxed for 5 h, allowed to cool to room temperature, poured into saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc until extraction was complete (TLC control, silica, 3:7 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 18 cm), using 3:7 EtOAc-hexane, gave lactone **31** (47.2 mg, 48% over two steps) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1766 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.41-1.55 (m, 1 H), 1.75-2.06 (m, 4 H), 2.30-2.45 (m, 1 H), 2.51-2.63 (m, 1 H), 2.66-2.80 (m, 1 H), 3.45-3.65 (m, 2 H), 4.85-4.95 (m, 1 H), 7.30-7.46 (m, 6 H), 7.55-7.65 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.2 (s'), 26.8 (q'), 27.1 (t'), 31.9 (t'), 35.5 (t'), 42.0 (d'), 48.6 (d'), 65.9 (t'), 86.5 (d'), 127.7 (d'), 129.8 (d'), 133.4 (s'), 135.5 (d'), 177.4 (s'); exact mass *m/z*

calcd for $C_{24}H_{30}O_3NaSi$ (M+Na) 417.1862, found 417.1862.

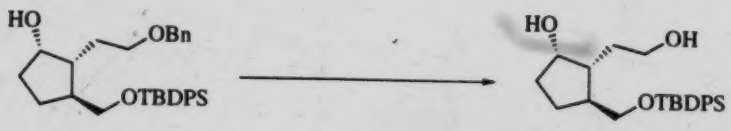
(3aα,4β,6aα)-(±)-Hexahydro-4-(hydroxymethyl) cyclopenta-[*b*]furan-2-one (9).



31 **9**

TBAF (1.0 M in THF, 0.18 mL, 0.18 mmol) was added dropwise to a stirred solution of lactone **31** (35.2 mg, 0.089 mmol) in dry THF (5 mL). After 48 h, water (5 mL) was added and the aqueous solution was extracted with EtOAc until extraction was complete (TLC control, silica, EtOAc). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.0 × 15 cm), using EtOAc, gave alcohol **9** (13.0 mg, 93%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1767, 3427 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.41-1.58 (m, 1 H), 1.72 (s, 1 H), 1.80-2.05 (m, 4 H), 2.32-2.45 (m, 1 H), 2.52-2.65 (m, 1 H), 2.70-2.85 (m, 1 H), 3.45-3.63 (m, 2 H), 4.90-5.0 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.0 (t'), 31.9 (t'), 35.6 (t'), 41.9 (d'), 48.6 (d'), 64.9 (t'), 86.6 (d'), 177.6 (s'); exact mass *m/z* calcd for $C_8H_{12}O_3$ 156.0786, found 156.0788.

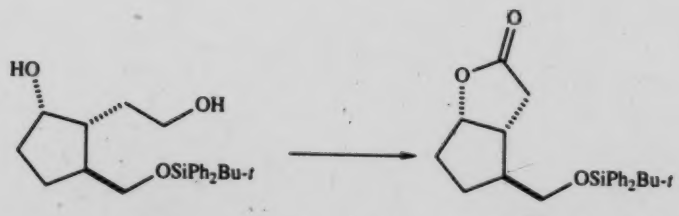
(1α,2α,3β)-(±)-3-[[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-methyl]-2-[2-hydroxyethyl]cyclopentanol (30).



24 **30**

Pd/C (10%, *ca.* 8 mg) was added to a solution of **24** (75.8 mg, 0.16 mmol) in bench MeOH (10 mL). The mixture was stirred under a H_2 atmosphere (balloon) for 7 h, filtered through a short pad (0.5 × 1 cm) of Celite, and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1 × 18 cm), using EtOAc, gave diol **30** (56.3 mg, 91%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3334 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 1.07 (s, 9 H), 1.38-2.10 (m, 8 H), 2.74 (br s, 2 H), 3.49-3.82 (m, 4 H), 4.19-4.35 (m, 1 H), 7.29-7.52 (m, 6 H), 7.58-7.81 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.3 (s'), 26.0 (t'), 26.9 (q'), 30.9 (t'), 33.4 (t'), 44.8 (d'), 46.6 (d'), 62.1 (t'), 66.3 (t'), 74.8 (d'), 127.6 (d'), 129.6 (d'), 133.8 (s'), 135.6 (d'); exact mass *m/z* calcd for $C_{24}H_{34}O_3NaSi$ (M+Na) 421.2175, found 421.2181.

(3aα,4β,6aα)-(±)-4-[[[(1,1-Dimethylethyl)diphenyl silyl]-oxy]methyl]hexahydrocyclopenta[*b*]furan-2-one (31).



30 **31**

$KMnO_4$ (0.2 g, 1.27 mmol) and $CuSO_4 \cdot 5H_2O$ (0.02 g, 0.08 mmol) were added consecutively to a stirred solution of diol **30** (31.9 mg, 0.080 mmol) in dry CH_2Cl_2 (5 mL). After 16 h, the heterogeneous mixture was filtered through a short pad (0.5 × 0.5 cm) of Celite, and evaporated. Flash chromatography of the residue over silica gel (1 × 16 cm), using 3:7 EtOAc-hexane, gave lactone **31** (16.5 mg, 52%) as a pure (^{1}H NMR, 400 MHz), colorless oil, spectroscopically identical to material obtained earlier.

Ethyl 3-[[(1,1-Dimethylethyl)silyl]oxy]-4-pentenoate (71).

70 **71**

Imidazole (2.982 g, 43.8 mmol) and *t*-$BuMe_2SiCl$ (3.961 g, 26.3 mmol) were added consecutively to a stirred solution of

70 (2.891 g, 21.9 mmol) in dry CH_2Cl_2 (150 mL). After 3 h, water (75 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.5 × 20 cm), using 1:9 EtOAc-hexane, gave protected alcohol **71** (5.27 g, 93%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 3 H), 0.04 (s, 3 H), 0.85 (s, 9 H), 1.25 (t, J = 7.2 Hz, 3 H), 2.42 (dd, J = 14.5, 5.2 Hz, 1 H), 2.50 (dd, J = 14.5, 8.1 Hz, 1 H), 4.02-4.18 (m, 2 H), 4.5-4.6 (m, 1 H), 5.05 (dt, J = 10.3, 1.3 Hz, 1 H), 5.20 (dt, J = 17.1, 1.5 Hz, 1 H), 5.75-5.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -5.2 (q'), -4.5 (q'), 14.1 (q'), 18.0 (s'), 25.6 (q'), 43.7 (t'), 60.3 (t'), 70.8 (d'), 114.5 (t'), 140.3 (d'), 171.0 (s'). Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.28; H, 10.17.

6-[[(1,1-Dimethylethyl)silyl]oxy]-1-(phenylmethoxy)-7-octen-2-yn-4-one (72).

71 **72**

n-BuLi (2.5 M in hexanes, 10.05 mL, 25 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of benzyl propargyl ether (3.67 g, 25.1 mmol) in dry THF (20 mL).

After 30 min, the cold bath was removed and the solution was allowed to warm to room temperature. In a separate round-bottomed flask, $BF_3 \cdot OEt_2$ (2.76 mL, 22.5 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **71** (5.27 g, 20.4 mmol) in dry THF (30 mL). The lithium acetylide solution (now at room temperature) was added dropwise to the stirred and cooled solution of **71**. Stirring at -78 °C was continued for 2 h, and the mixture was poured into water (150 mL). The aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Crude **72** co-eluted with benzyl propargyl ether and so was not characterized, but used directly in the next step.

6-Hydroxy-1-(phenylmethoxy)-7-octen-2-yn-4-one (73).

72 **73**

HF (48% in water, 1.41 mL, 41 mmol) was added in one lot to a solution of the crude product (**72**) from the previous reaction in MeCN (100 mL). After 5 h, saturated aqueous $NaHCO_3$ (100 mL) was added dropwise from a separatory funnel. EtOAc (50 mL) was added and the aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 2:3 EtOAc-hexane). The combined organic extracts

were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.5 × 17 cm), using 2:3 EtOAc-hexane, gave alcohol **73** (2.326 g, 47% over two steps) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1675, 3447 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.51 (br s, 1 H), 2.81 (d, *J* = 6.1 Hz, 2 H), 4.31 (s, 2 H), 4.52-4.75 (m, 3 H), 5.15 (dt, *J* = 10.5, 1.3 Hz, 1 H), 5.29 (dt, *J* = 17.2, 1.4 Hz, 1 H) 5.85 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1 H), 7.22-7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 51.8 (t'), 56.9 (t'), 68.4 (d'), 72.2 (t'), 85.2 (s'), 89.0 (s'), 115.6 (t'), 128.1 (d'), 128.2 (d'), 128.5 (d'), 136.6 (s'), 138.5 (d'), 185.7 (s'); Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.55; H, 6.63.

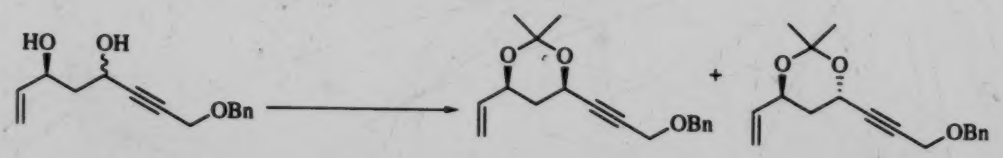
(3*R,5*S**)- and (3*R**,5*R**)-(±)-8-Phenylmethoxy-1-octen-6-yn-3,5-diol (74, 84).**

73 **74, 84**

DIBAL (1.0 M in PhMe, 15.3 mL, 15.3 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **73** (1.488 g, 6.10 mmol) in dry THF (80 mL). After 40 minutes, MeOH (4 mL), $Na_2SO_4 \cdot 10H_2O$ (4 g), Celite (6.3 g), and water (2 mL) were added sequentially to the cold (-78 °C). The cold bath was removed and stirring was continued for an additional 30 min. The mixture was then filtered through a pad (7 × 4

cm) of Celite, EtOAc being used to elute all of the product (TLC control, silica, 1:1 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 17 cm), using 1:1 EtOAc-hexane, gave diols **74** and **84** (1.346 g, 90%) as an inseparable mixture of diastereomers. The ratio of the two diols could not be calculated from the ^{1}H NMR spectrum, and both isomers were used directly in the next step.

(4*R,6*S**)- and (4*R**,6*R**)-(±)-4-Ethenyl-6-[3-phenylmethoxy-1-propynyl]-2,2-dimethyl-1,3-dioxane (75, 76).**

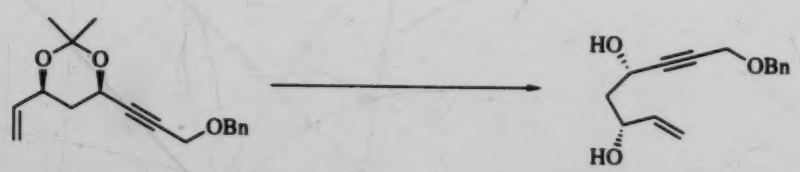


74, 84 **75** **76**

2,2-Dimethoxypropane (6.73 mL, 54.7 mmol) and PPTS (*ca.* 10 mg) were added consecutively to a stirred solution of **74** and **84** in dry CH_2Cl_2 (15 mL). After 6 h, the solution was poured into saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 22 cm), using first 1:19 EtOAc-hexane, and then 1:9 EtOAc-hexane, gave **75** (1.370 g, 88%) as a pure (^{1}H NMR, 400 MHz), colorless oil, and the minor diastereomer (**76**) (92.6 mg, 6%), which was discarded. Compound **75** had: FTIR (CH_2Cl_2 cast) 1200 cm^{-1}; ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 1.46 (s, 3 H), 1.50 (s, 3 H), 1.68-1.83 (m, 2 H), 4.2 (s, 2 H), 4.3-4.39 (m, 1 H), 4.58 (s, 2 H), 4.72-4.79 (m, 1 H), 5.12-5.18 (m, 1 H), 5.22-5.30 (m, 1 H), 5.73-5.86 (m, 1 H), 7.23-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.3 (q'), 30.0 (q'), 36.9 (t'), 57.4 (t'), 60.1 (d'), 69.6 (d'), 71.6 (t'), 80.7 (s'), 84.9 (s'), 99.3 (s'), 115.9 (t'), 127.8 (d'), 127.9 (d'), 128.4 (d'), 137.3 (s') 137.7 (d'); exact mass *m/z* calcd for $C_{18}H_{22}O_3$ 286.1569, found 286.1531. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.82; H, 7.57.

(3*R,5*S**)-(±)-8-Phenylmethoxy-1-octen-6-yn-3,5-diol (84).**

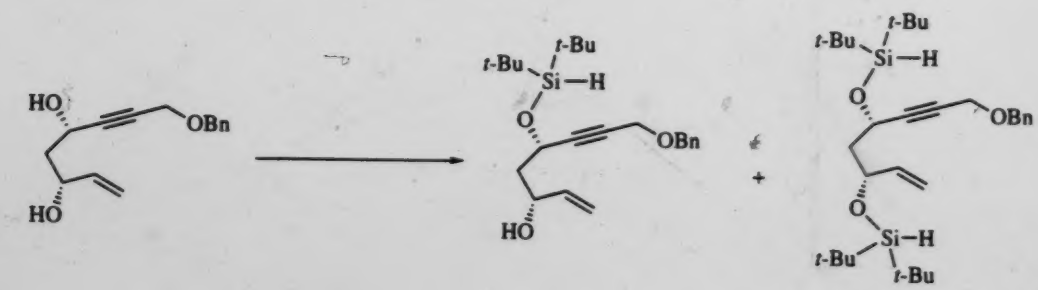


75 **84**

CF_3CO_2H (1.0 mL, 13 mmol) was added to a stirred solution of **75** (2.27 g, 7.94 mmol) in THF (45 mL) and water (5 mL). After 4 h, the solution was titrated with saturated aqueous $NaHCO_3$ until basic (pH paper). The aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 3:2 EtOAc-hexane), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 16 cm), using 3:2 EtOAc-hexane, gave diol **84**

(1.818 g, 93%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3374 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88-2.03 (m, 2 H), 2.49 (br s, 2 H), 4.20 (s, 2 H), 4.35-4.43 (m, 1 H), 4.58 (s, 2 H), 4.66-4.72 (m, 1 H), 5.13 (dt, *J* = 10.4, 1.3 Hz, 1 H), 5.27 (dt, *J* = 17.1, 1.4 Hz, 1 H), 5.88 (ddd, *J* = 16.9, 7.1, 6.0 Hz, 1 H), 7.25-7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 43.7 (t'), 57.2 (t'), 61.2 (d'), 71.5 (t'), 71.6 (d'), 80.6 (s'), 87.1 (s'), 114.8 (t'), 127.8 (d'), 128.0 (d'), 128.3 (d'), 137.0 (s'), 139.9 (d'); exact mass *m/z* calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1241.

(3*R,5*S**)-(±)-5-[[Bis[(1,1-dimethyl)ethyl]]silyl]oxy]-8-phenylmethoxy-1-octen-6-yn-3-ol (85) and (3*R**,5*S**)-(±)-[[5-[[[Bis[(1,1-dimethyl)ethyl]]silyl]oxy]-8-phenyl-methoxy-1-octen-6-ynyl]oxy][bis[(1,1-dimethyl)ethyl]]-silane (86).**



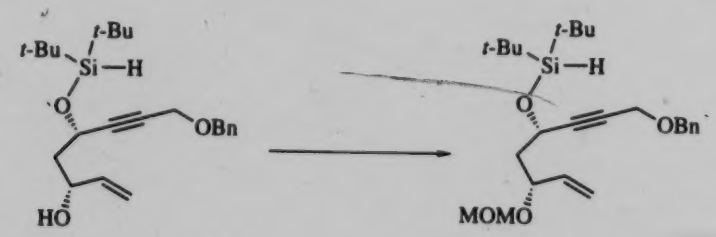
84 **85** **86**

Imidazole (496.3 mg, 7.29 mmol) and *t*-Bu_2SiHCl (0.92 mL, 4.56 mmol) were added consecutively to a stirred solution of **84** (1.043 g, 3.65 mmol) in dry THF (30 mL). After 20 min,

water (30 mL) was added, and the mixture was extracted with EtOAc until extraction was complete (TLC control, silica, 1:3 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 19 cm), using first 1:19 EtOAc-hexane, and then 1:1 EtOAc-hexane, gave alcohol **85** (1.124 g, 79%, 91% based on recovered starting material), compound **86** (91.3 mg, 4%), and starting substrate (**84**) (263.1 mg) as pure (^1H NMR, 400 MHz), colorless oils. Compound **85** had: FTIR (CH_2Cl_2 cast) 2096, 3450 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.30 (s, 9 H), 1.50 (s, 9 H), 1.92 (t, J = 6.0 Hz, 2 H), 2.76 (d, J = 3.5 Hz, 1 H), 4.16 (s, 1 H), 4.22 (d, J = 2.0 Hz, 2 H), 4.48-4.65 (m, 3 H), 4.80-4.88 (m, 1 H), 5.11 (dt, J = 10.5, 1.8 Hz, 1 H), 5.29 (dt, J = 17.5, 1.9 Hz, 1 H), 5.82-5.97 (m, 1 H), 7.20-7.42 (m, 5 H) Irradiation at δ 4.22 caused the multiplet at δ 4.84 to collapse to a triplet (J = 5.5 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.5 (s'), 20.1 (s'), 27.2 (q'), 27.6 (q'), 45.0 (t'), 57.2 (t'), 65.0 (d'), 70.7 (d'), 71.4 (t'), 81.9 (s'), 86.6 (s'), 114.5 (t'), 127.8 (d'), 128.0 (d'), 128.4 (d'), 137.4 (s'), 140.3 (d'); exact mass m/z calcd for $C_{15}H_{19}O_3Si$ (M-C_8H_{17}) 275.1104, found 275.1105. Compound **86** had: FTIR (CH_2Cl_2 cast) 2092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.89-1.10 (m, 36 H), 1.78-1.89 (m, 1 H), 2.04-2.13 (m, 1 H), 4.05 (s, 1 H), 4.15 (s, 1 H), 4.23 (s, 2 H), 4.41-4.49 (m, 1 H), 4.60 (s, 2 H), 4.66-4.72 (m, 1 H), 5.10 (dt, J = 10.2, 1.2 Hz, 1 H), 5.18 (dt, J = 17.4, 2.0 Hz, 1 H), 5.79 (ddd, J = 17.0,

11.1, 10.9 Hz, 1 H), 7.25-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.7 (s'), 19.9 (s'), 20.0 (s'), 20.2 (s'), 27.3 (q'), 27.4 (q'), 47.1 (t'), 57.3 (t'), 63.6 (d'), 71.3 (t'), 73.9 (d'), 81.4 (s'), 87.4 (s'), 115.4 (t'), 127.8 (d'), 128.1 (d'), 128.4 (d'), 137.6 (s'), 140.2 (d'). Anal. Calcd for $C_{31}H_{54}O_3Si_2$: C, 70.13; H, 10.25. Found: C, 70.03; H, 10.42.

(4*R,6*S**)-(±)-6-[(Methoxy)methoxy]-1-phenylmethoxy-7-octen-2-ynyl]oxy][bis[(1,1-dimethyl)ethyl]]silane (88).**

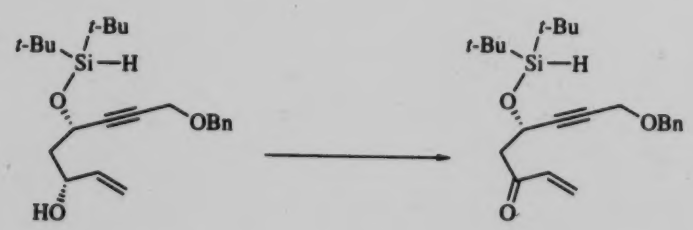


85 **88**

i-Pr_2NEt (1.06 mL, 6.1 mmol) and $MeOCH_2Cl$ (0.38 mL, 5.1 mmol) were added consecutively to a stirred and cooled (0 °C) solution of **85** (785.1 mg, 2.02 mmol) in dry CH_2Cl_2 (20 mL). After 1 h, the ice bath was removed and stirring was continued for an additional 6 h. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 18 cm), using 1:9 EtOAc-hexane, gave compound **88** (778.2 mg, 89%) as a pure (^1H NMR, 400 MHz),

colorless oil: FTIR (CH_2Cl_2 cast) 2092 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.0 (s, 9 H), 1.04 (s, 9 H), 1.85 (ddd, *J* = 13.5, 8.3, 4.8 Hz, 1 H), 2.09 (ddd, *J* = 13.4, 8.8, 6.1 Hz, 1 H), 3.37 (s, 3 H), 4.13 (s, 1 H), 4.22 (s, 2 H), 4.24-4.32 (m, 1 H), 4.52 (d, *J* = 6.7 Hz, 1 H), 4.60 (s, 2 H), 4.65-4.74 (m, 2 H), 5.17-5.28 (m, 2 H), 5.69 (ddd, *J* = 17.3, 10.3, 7.7 Hz, 1 H), 7.24-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.7 (s'), 19.9 (s'), 27.2 (q'), 44.3 (t'), 55.4 (q'), 57.2 (t'), 63.6 (d'), 71.2 (t'), 74.1 (d'), 81.4 (s'), 86.9 (s'), 93.6 (t'), 117.8 (t'), 127.8 (d'), 128.0 (d'), 128.4 (d'), 137.5 (s'), 137.6 (d'); exact mass *m/z* calcd for $C_{25}H_{40}O_4Si$ 432.2696, found 432.2695.

(±)-8-Phenylmethoxy-5-[[bis[(1,1-dimethyl)ethyl] silyl]-oxy]-1-octen-6-yn-3-one (87).

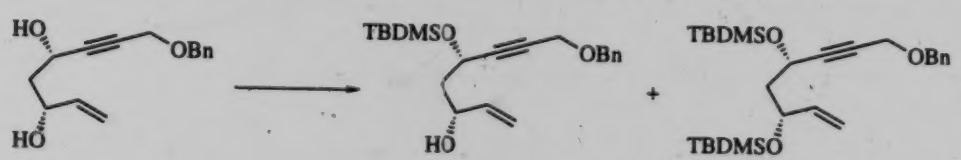


85 **87**

Molecular sieves (4Å, 35 mg) and PCC (106 mg, 0.49 mmol) were added consecutively to a stirred solution of **85** (95.4 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL). After 6 h, the brown mixture was filtered through a pad (2 × 2 cm) of silica gel, the desired compound being eluted with 1:1 EtOAc-hexane (TLC control, silica, 1:4 EtOAc-hexane). Evaporation of the

solvent and flash chromatography of the residue over silica gel (2 × 17 cm), using 1:9 EtOAc-hexane, gave ketone **87** (52.9 mg, 56%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1687, 2102 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.0 (s, 9 H), 1.1 (s, 9 H), 2.95 (dd, *J* = 15.8, 5.8 Hz, 1 H), 3.17 (dd, *J* = 15.8, 7.3 Hz, 1 H), 4.16 (s, 1 H),4.20 (d, *J* = 1.5 Hz, 2 H), 4.46 (s, 2 H), 5.05-5.10 (m, 1 H), 5.90 (dd, *J* = 10.6, 1.0 Hz, 1 H), 6.25 (dd, *J* = 17.7, 1.0 Hz, 1 H), 6.40 (dd, *J* = 17.7, 10.6 Hz, 1 H), 7.27-7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.6 (s'), 20.0 (s'), 27.2 (q'), 47.8 (t'), 57.2 (t'), 62.3 (d'), 71.3 (t'), 81.2 (s'), 86.6 (s'), 127.8 (d'), 128.1 (d'), 128.4 (d'), 129.0 (t'), 137.0 (d'), 137.4 (s'), 197.1 (s'); exact mass *m/z* calcd for $C_{19}H_{25}O_3Si$ ($M-C_4H_9$) 329.1573, found 329.1571.

(3*R,5*S**)-(±)-5-[[dimethyl[(1,1-dimethyl)ethyl]silyl]oxy]-8-phenylmethoxy-1-octen-6-yn-3-ol (90) and (3*R**,5*S**)-(±)-[5-[[[dimethyl[(1,1-dimethyl)ethyl]silyl]oxy]-8-phenyl-methoxy-1-octen-6-ynyl]oxy][dimethyl[(1,1-dimethyl)-ethyl]]silane (90b).**

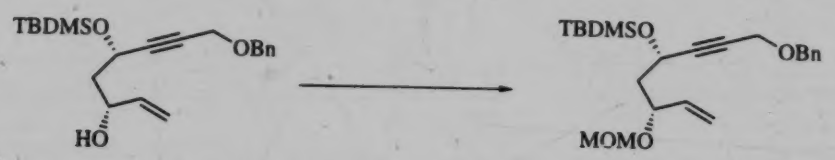


84 **90** **90b**

Imidazole (2.247 g, 33.0 mmol) and *t*-$BuMe_2SiCl$ (2.736 g, 18.2 mmol) were added consecutively to a stirred solution of **84** (4.06 g, 16.5 mmol) in dry CH_2Cl_2 (200 mL). After 20 min,

the reaction was quenched by addition of water (100 mL) (The reaction time represents the point at which formation of di-silylated product becomes a competing reaction). The aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 3:2 EtOAc-hexane), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 19 cm), using first 1:9 EtOAc-hexane, and then 3:2 EtOAc-hexane, gave alcohol **90** (2.811 g, 47%, 82% based on recovered starting material) as a pure (^1H NMR, 400 MHz), colorless oil, starting diol **84** (1.710 g), and di-silylated product **90b** (410.6 mg). Compound **90** had: FTIR (CH_2Cl_2 cast) 3432 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.18 (s, 3 H), 0.20 (s, 3 H), 0.91 (s, 9 H), 1.86-2.05 (m, 2 H), 2.69 (br s, 1 H), 4.19 (d, J = 1.5 Hz, 2 H), 4.30-4.39 (m, 1 H), 4.58 (s, 2 H), 4.63-4.70 (m, 1 H), 5.11 (dt, J = 10.4, 1.4 Hz, 1 H), 5.28 (dt, J = 17.3, 1.5 Hz, 1 H), 5.87 (ddd, J = 17.1, 10.5, 5.8 Hz, 1 H), 7.24-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -5.0 (q'), -4.3 (q'), 18.1 (s'), 25.7 (q'), 45.1 (t'), 57.3 (t'), 62.3 (d'), 71.2 (d'), 71.5 (t'), 81.1 (s'), 87.4 (s'), 114.6 (t'), 127.9 (d'), 128.0 (d'), 128.4 (d'), 137.4 (s'), 140.2 (d'); exact mass *m/z* calcd for $C_{17}H_{23}O_3Si$ ($M-C_4H_9$) 303.1417, found 303.1423.

(4*R,6*S**)-(±)-6-[(Methoxy)methoxy]-1-phenylmethoxy-7-octen-2-ynyl]oxy][dimethyl[1,1-dimethylethyl]]silane (91).**



90 **91**

i-Pr_2NEt (2.34 mL, 13.4 mmol) and $MeOCH_2Cl$ (1.02 mL, 13.4 mmol) were added consecutively to a stirred and cooled (0 °C) solution of **90** (1.612 g, 4.48 mmol) in dry CH_2Cl_2 (50 mL). After 1 h, the ice bath was removed and stirring was continued for an additional 9 h. Water (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 × 16 cm), using 1:9 EtOAc-hexane, gave **91** (1.563 g, 86%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1318 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.12 (s, 3 H), 0.18 (s, 3 H), 0.91 (s, 9 H), 1.75-1.92 (m, 1 H), 1.96-2.14 (m, 1 H), 3.38 (s, 3 H), 4.14-4.33 (m, 3 H), 4.47-4.74 (m, 5 H), 5.12-5.30 (m, 2 H), 5.55-5.79 (m, 1 H), 7.25-7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -5.0 (q'), -4.4 (q'), 18.1 (s'), 25.7 (q'), 44.4 (t'), 55.3 (q'), 57.2 (t'), 60.2 (d'), 71.2 (t'), 74.1 (d'), 80.6 (s'), 87.6 (s'), 93.6 (t'), 117.8 (t'), 127.7 (d'), 127.9 (d'), 128.3 (d'), 137.4

(s'), 137.5 (d'). Anal. Calcd for $C_{23}H_{36}O_4Si$: C, 68.27; H, 8.97. Found: C, 67.93; H, 9.21.

(2*R,3*S**,5*R**)-(±)- and (2*R**,3*R**,5*S**)-(±)-5-[[Dimethyl(1,1-dimethyl)ethylsilyl]oxy]-3-[(methoxy)methoxy]-8-phenyl-methoxy-6-octyn-1,2-diol (92a,b).**

91 **92a,b**

4-Methylmorpholine *N*-oxide (644.9 mg, 5.50 mmol) and OsO_4 (2.5% in *t*-BuOH, 1.86 g, 0.18 mmol) were added consecutively to a stirred solution of **91** (741.5 mg, 1.83 mmol) in THF (90 mL) and water (10 mL). After 20 h, $Na_2S_2O_3$ (1.0 M, 30 mL) was added, the mixture was stirred for 15 min, and the aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 3:1 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 3:1 EtOAc-hexane, gave diols **92a,b** (429.6 mg, 54%) as an inseparable mixture of diastereomers: FTIR (CH_2Cl_2 cast) 3432 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 3 H), 0.17 (s, 3 H), 0.89 (s, 9 H), 1.86-2.10 (m, 4 H), 3.40 (s, 3 H), 3.58-3.95 (m, 4 H), 4.20 (s, 2 H), 4.58 (s, 2 H), 4.60-4.72 (m, 3 H), 7.23-7.39

(m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) (only the signals for the major isomer are given) δ -5.0 (q'), -4.5 (q'), 18.1 (s'), 25.7 (q'), 40.4 (t'), 56.0 (q'), 57.3 (t'), 60.4 (d'), 63.2 (t'), 71.5 (t'), 73.2 (d'), 78.8 (d'), 81.4 (s'), 87.1 (s'), 97.5 (t'), 127.9 (d'), 128.0 (d'), 128.4 (d'), 137.4 (s'); exact mass *m/z* calcd for $C_{22}H_{35}O_5Si$ ($M-OCH_3$) 407.2254, found 407.2258.

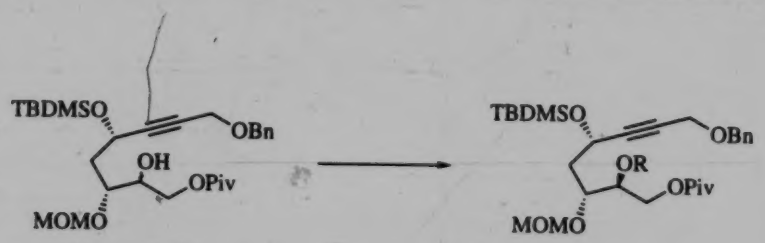
(2*R,3*S**,5*R**)- and (2*R**,3*R**,5*S**)-(±)-5-[[Dimethyl(1,1-dimethyl)ethylsilyl]oxy]-2-hydroxy-3-(methoxymethoxy)-6-octyn-1-yl 1,1-Dimethylpropionate (93a,b).**

92a,b **93a,b**

DMAP (406.7 mg, 3.33 mmol) and *t*-BuCOCl (0.21 mL, 1.66 mmol) were added consecutively to a stirred and cooled (0 °C) solution of **92a,b** (662.8 mg, 1.51 mmol) in dry PhMe (25 mL). The ice bath was removed and, after 1 h, water (25 mL) was added. The aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 1:4 EtOAc-hexane), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 17 cm), using 1:9 EtOAc-hexane, gave diastereomeric alcohols **93a,b** (348.2 mg, 44%) as an inseparable mixture: FTIR (CH_2Cl_2 cast) 1730, 3445 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.14 (s, 3 H), 0.18 (s, 3 H), 0.90

(s, 9 H), 1.20 (s, 9 H), 1.88-1.95 (m, 1 H), 2.05-2.13 (m, 1 H), 3.30-3.42 (m, 4 H; includes a singlet at δ 3.39, 3 H), 3.76-3.91 (m, 2 H), 4.09-4.23 (m, 4 H), 4.58 (s, 2 H), 4.60-4.72 (m, 3 H), 7.24-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) (signals indicated are for the major diastereomer only) δ -5.3 (q'), -4.7 (q'), 17.9 (s'), 25.5 (q'), 26.9 (q'), 38.5 (s'), 39.8 (t'), 55.8 (q'), 57.1 (d'), 60.2 (t'), 71.2 (d'), 71.3 (t'), 78.4 (d'), 81.1 (s'), 86.9 (s'), 97.2 (t'), 127.6 (d'), 127.8 (d'), 128.2 (d'), 137.2 (s'), 178.4 (s').

(2*R,3*S**,5*R**)-(±)-5-[[Dimethyl(1,1-dimethyl)ethylsilyl]-oxy]-2-[(4-fluorophenoxy)thiocarbonyl-oxy]-3-(methoxy-methoxy)-6-octyn-1-yl 1,1-Dimethylpropionate (94).**



93a,b **94**

Dry pyridine (0.081 mL, 1.00 mmol), DMAP (40.7 mg, 0.33 mmol), and *p*-$FC_6H_4OC(S)Cl$ (0.28 mL, 2.0 mmol) were added consecutively to a stirred solution of **93a,b** (348.2 mg, 0.67 mmol) in dry CH_2Cl_2 (12 mL). After 18 h, saturated aqueous NH_4Cl (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 18 cm),

using 1:9 EtOAc hexane, gave **94** (324.6 mg, 72%) as a pure (^{1}H NMR, 400 MHz), colorless oil. The stereochemistry of **94** was unknown; the stereochemistry indicated is arbitrary: FTIR (CH_2Cl_2 cast) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 3 H), 0.17 (s, 3 H), 0.90 (s, 9 H), 1.20 (s, 9 H), 1.94-2.12 (m, 2 H), 3.42 (s, 3 H), 4.21 (s, 2 H), 4.22-4.32 (m, 1 H), 4.32-4.51 (m, 2 H), 4.57 (s, 2 H), 4.6-4.68 (m, 1 H), 4.71 (s, 2 H), 5.71-5.80 (m, 1 H), 6.95-7.08 (m, 4 H), 7.24-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -5.0 (q'), -4.5 (q'), 18.1 (s'), 25.8 (q'), 27.1 (q'), 38.8 (s'), 40.5 (t'), 56.1 (q'), 57.3 (t'), 60.3 (d'), 61.6 (t'), 71.5 (t'), 73.3 (d'), 81.5 (s'), 83.7 (d'), 86.8 (s'), 96.5 (t'), 116.0 (d'), 116.5 (d'), 123.3 (d'), 123.4 (d'), 127.8 (d'), 128.1 (d'), 128.4 (d'), 137.4 (s'), 149.2 (s'), 158.2 (s'), 163.1 (s'), 178.1 (s'), 194.7 (s') (the ^{13}C NMR spectrum contains some additional peaks due to ^{19}F coupling); exact mass *m/z* calcd for $C_{35}H_{49}O_8FSSi$ 676.2902, found 676.2892.

(2*R,3*S**,5*R**)-(±)-2-[(4-Fluorophenoxy)-thiocarbonyloxy]-5-hydroxy-3-(methoxymethoxy)-6-octyn-1-yl 1,1-Dimethyl-propionate (94b).**

94 **94b**

HF (48% in water, 0.5 mL, 14.5 mmol) was added to a

solution of **94** [R = *p*-$FC_6H_4OC(S)$] (297.3 mg, 0.44 mmol) in MeCN (10 mL). After 2 h, saturated aqueous $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 3:7 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 14 cm), using 3:7 EtOAc-hexane, gave **94b** (216.1 mg, 87%), which was not characterized but used directly in the next step.

(2*R,3*S**,5*R**)- and (2*R**,3*R**,5*S**)-(±)-2-[(4-Fluorophenoxy)-thiocarbonyloxy]-5-[[bis(1,1-dimethyl)ethylsilyl]oxy]-3-(methoxymethoxy)-6-octyn-1-yl 1,1-Dimethylpropionate (95).**

94b **95**

Imidazole (52.4 mg, 0.77 mmol) and *t*-Bu_2SiHCl (0.10 mL, 0.50 mmol) were added consecutively to a stirred solution of **94b** (216.1 mg, 0.38 mmol) in dry THF (20 mL). After 10 h, water (15 mL) was added and the aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash

chromatography of the residue over silica gel (2 × 14 cm), using 1:9 EtOAc-hexane, gave **95** (251.7 mg, 93%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1736, 2095 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.99 (s, 9 H), 1.04 (s, 9 H), 1.18 (s, 9 H), 1.92-2.23 (m, 2 H), 3.41 (s, 3 H), 4.12 (s, 1 H), 4.22 (d, *J* = 1.3 Hz, 2 H), 4.25 - 4.34 (m, 1 H), 4.38 (dd, *J* = 12.3, 7.7 Hz, 1 H), 4.49 (dd, *J* = 12.2, 3.3 Hz, 1 H), 4.56 (s, 2 H), 4.61-4.70 (m, 1 H), 4.71 (s, 2 H), 5.65-5.79 (m, 1 H), 6.89-7.06 (m, 4 H), 7.19-7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.7 (s'), 20.0 (s'), 27.1 (q'), 27.2 (q'), 38.8 (s'), 40.2 (t'), 56.1 (q'), 57.3 (t'), 61.6 (t'), 63.8 (d'), 71.4 (t'), 73.4 (d'), 82.3 (s'), 83.6 (d'), 86.1 (s'), 96.7 (t'), 116.0 (d'), 116.4 (d'), 123.2 (d'), 123.4 (d'), 127.8 (d'), 128.1 (d'), 128.4 (d'), 137.4 (s'), 149.2 (s'), 158.2 (s'), 163.0 (s'), 178.0 (s'), 194.6 (s') (the ^{13}C spectrum contains some additional peaks due to ^{19}F coupling); exact mass *m/z* calcd for $C_{33}H_{44}O_8FSSi$ ($M-C_4H_9$) 647.2510, found 647.2522.

(3α,3aβ,4α,5α,6aβ)- and (3α,3aβ,4β,5α,6aβ)-(±)-2,2-Bis-(1,1-dimethylethyl)hexahydro-5-methoxymethoxy-3-[(phenyl-methoxy)methyl]-2*H*-cyclopent[*d*]-[1,2] oxasilol-4-ylmethyl-1,1-Dimethylpropionate (96a,b).

95 **96a,b**

A solution of Bu_3SnH (77.6 μL, 0.29 mmol) and AIBN (11.8 mg, 0.07 mmol) in dry PhMe (6 mL) was added over 6 h (syringe pump) to a stirred and heated (100 °C) solution of **95** (127 mg, 0.18 mmol) in dry PhMe (60 mL). Stirring at 100 °C was continued for an additional 1 h after the end of the addition. The mixture was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (1 × 18 cm), using 1:9 EtOAc-hexane, gave cyclized compounds **96a,b** (76.1 mg, 79%) as an inseparable mixture. The ratio of the diastereomers could not be calculated from the ^1H NMR spectrum; however, the relative intensities of the ^{13}C NMR peaks indicated preferential formation of one of the isomers. The compounds were not fully characterized, but were used directly in the next step.

(1α,2β,3β,5β)-(±)-3-hydroxy-2-[2-(phenylmethoxy)ethyl] -5-(methoxymethoxy)cyclopentylmethyl 1,1-Dimethyl propionate (97).

96a,b **97**

TBAF (1.0 M in THF, 1.42 mL, 1.42 mmol) was added dropwise to a stirred solution of **96a,b** (76.1 mg, 0.14 mmol) in THF (3 mL) and DMF (3 mL). The solution was heated at 70 °C for 2 h, and cooled to room temperature. Water (10 mL) was added, and the aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 1:1 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated, residual DMF being removed under oil pump vacuum (*ca.* 0.1 mmHg). Flash chromatography of the residue over silica gel (1 × 14 cm), using 2:3 EtOAc-hexane, gave alcohol **97** (49.3 mg, 88%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1727, 3507 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.19 (s, 9 H), 1.60-1.70 (m, 1 H), 1.74-1.98 (m, 3 H), 2.0-2.12 (m, 2 H), 2.75 (d, J = 6.0 Hz, 1 H), 3.32 (s, 3 H), 3.49-3.58 (m, 1 H), 3.60-3.69 (m, 1 H), 3.92-4.08 (m, 2 H), 4.08-4.19 (m, 2 H), 4.51 (s, 2 H), 4.63 (s, 2 H), 7.24-7.40 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 27.3 (q'), 28.9 (t'), 39.1 (s'), 40.2

(t'), 45.3 (d'), 49.7 (d'), 55.5 (d'), 64.3 (t'), 70.2 (t'), 73.3 (q'), 73.5 (t'), 79.8 (d'), 95.8 (t'), 128.0 (d'), 128.1 (d'), 128.7 (d'), 138.8 (s'), 178.6 (s'); exact mass *m/z* calcd for $C_{22}H_{34}O_6Na$ (M+Na) 417.2253, found 417.2258.

(1α,2β,3β,5β)-(±)-3-hydroxy-2-(2-hydroxyethyl)-5-(methoxy-methoxy)cyclopentylmethyl 1,1-Dimethyl propionate (98).

97 **98**

Pd/C (10%, ca. 3 mg) was added to a solution of **97** (35.2 mg, 0.089 mmol) in bench MeOH (4 mL). The mixture was stirred under a H_2 atmosphere (balloon) for 1 h, and filtered through a pad (1 × 1 cm) of Celite, using EtOAc. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 10 cm), using EtOAc, gave **98** (23.6 mg, 87%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1729, 3425 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.18 (s, 9 H), 1.61-1.71 (m, 1 H), 1.71-1.82 (m, 1 H), 1.82-1.94 (m, 2 H), 1.97-2.07 (m, 1 H), 2.11 (ddd, *J* = 9.9, 9.8, 4.4 Hz, 1 H), 2.19 (br s, 1 H), 2.79 (br s, 1 H), 3.35 (s, 3 H), 3.61-3.80 (m, 2 H), 3.92-4.05 (m, 2 H, this includes a dd, *J* = 11.3, 6.1 Hz, 1 H, centered at 3.99), 4.11 (dd, *J* = 11.3, 4.6 Hz, 1 H), 4.20 (br s, 1 H), 4.62 (s, 2 H); ^{13}C NMR (CD_2Cl_2,

50.3 MHz) δ 27.3 (q'), 31.8 (t'), 39.1 (s'), 40.5 (t'), 45.4 (d'), 50.0 (d'), 55.6 (d'), 62.1 (t'), 64.6 (t'), 74.1 (q'), 80.1 (d'), 95.6 (t'), 178.7 (s'); exact mass *m/z* calcd for $C_{15}H_{27}O_5$ (M-OH) 287.1859, found 287.1857.

(3aα,4α,5β,6aα)-(±)-Hexahydro-5-methoxymethoxy-2-oxocyclopenta[*b*]furan-4-ylmethyl 1,1-Dimethylpropionate (99).

98 **99**

$KMnO_4$ (110 mg) and $CuSO_4 \cdot 5H_2O$ (11 mg) were added together to a stirred solution of diol **98** in CH_2Cl_2 (4 mL). The heterogeneous mixture was stirred vigorously for 12 h, and then filtered through a pad (2.5 × 1 cm) of Celite, using CH_2Cl_2. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 12 cm), using 1:1 EtOAc-hexane, gave lactone **99** (10.3 mg, 63%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1729, 1776 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.21 (s, 9 H), 2.05-2.20 (m, 1 H), 2.21-2.42 (m, 2 H), 2.51 (dd, *J* = 17.8, 2.4 Hz, 1 H), 2.59-2.71 (m, 1 H), 2.81 (dd, *J* = 17.8, 10.2 Hz, 1 H), 3.33 (s, 3 H), 3.93-4.10 (m, 3 H), 4.59 (q, *J* = 6.9 Hz, 2 H), 4.95 (ddd, *J* = 6.8, 6,8, 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.1 (q'), 35.4 (t'), 37.9 (t'), 38.8 (s'), 39.9 (d'), 51.6 (d'),

55.6 (q'), 63.9 (t'), 78.9 (d'), 83.5 (d'), 95.5 (t'), 176.6 (s'), 178.2 (s'); exact mass *m/z* calcd for $C_{15}H_{24}O_6Na$ (M+Na) 323.1471, found 323.1478.

Methyl (*E*)-5-Hydroxy-8-phenylmethoxy-2-octen-6-ynoate (40).

15 **40**

m-CPBA (2.094 g, 6.92 mmol) was added to a stirred and cooled (0 °C) solution of **15** (1.987 g, 4.61 mmol) in CH_2Cl_2 (125 mL). After 2 h, water (75 mL) was added. The aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 3:7 EtOAc-hexane), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.5 × 18 cm), using 3:7 EtOAc-hexane, gave **40** (1.048 g, 83%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 1723, 3431 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (br s, 1 H), 2.62 (ddd, *J* = 7.3, 6.1, 1.5 Hz, 2 H), 3.70 (S, 3 H), 4.21 (d, *J* = 1.7 Hz, 2 H), 4.51-4.61 (m, 3 H), 5.97 (dt, *J* = 15.7, 1.5 Hz, 1 H), 7.1 (dt, *J* = 15.7, 7.3 Hz, 1 H), 7.23-7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 40.1 (t'), 51.5 (q'), 57.2 (t'), 60.8 (d'), 71.6 (t'), 81.6 (s'), 86.3 (s'), 124.1 (d), 127.8 (d'), 128.0 (d'), 128.4 (d'), 137.1 (s'), 143.4 (d'), 166.6 (s'); exact mass *m/z* calcd for $C_{15}H_{15}O_3$ (M-

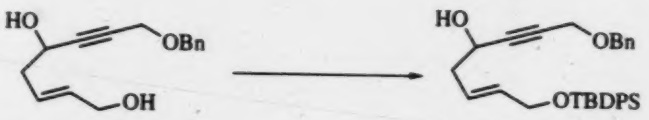
OCH_3) 243.1021, found 243.1040.

(*E*)-8-Phenylmethoxy-2-octen-6-yn-1,5-diol (59).

40 **59**

DIBAL (1.0 M in hexanes, 3.13 mL, 3.13 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **40** (342.9 mg, 1.25 mmol) in dry CH_2Cl_2 (50 mL). After 2.5 h, MeOH (2 mL), $Na_2SO_4 \cdot 10H_2O$ (2 g), Celite (5 g), and water (1 mL) were added sequentially to the cold (-78 °C) solution. The cold bath was removed, the mixture was stirred for an additional 1 h, and then filtered through a bed (3 × 20 cm) of Celite, using CH_2Cl_2. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 17 cm), using 1:1 EtOAc-hexane, gave **59** (267.0 mg, 87%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3362 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.96 (s, 2 H), 2.44-2.50 (m, 2 H), 4.07-4.15 (m, 2 H), 4.20 (d, *J* = 1.7 Hz, 2 H), 4.48 (dddd, *J* = 6.1, 6.1, 1.7, 1.7 Hz, 1 H), 4.58 (s, 2 H), 5.75-5.84 (m, 2 H), 7.24-7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 40.3 (t'), 57.2 (t'), 61.3 (d'), 62.9 (t'), 71.5 (t'), 80.6 (s'), 87.1 (s'), 126.8 (d'), 127.8 (d'), 128.0 (d'), 128.3 (d'), 133.1 (d'), 137.1 (s'); exact mass *m/z* calcd for $C_{15}H_{16}O_2$ (M-H_2O) 228.1150, found 228.1152.

(*E*)-8-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-phenyl-methoxy-6-octen-2-yn-4-ol (60).



59 **60**

Imidazole (146.3 mg, 2.15 mmol) and *t*-$BuPh_2SiCl$ (0.36 mL, 1.4 mmol) were added consecutively to a stirred solution of **59** (264.3 mg. 1.07 mmol) in dry CH_2Cl_2 (25 mL). After 2 h, water (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 1:9 EtOAc-hexane, gave **60** (488.1 mg, 94%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3404 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 9 H), 1.66 (br s, 1 H), 2.43-2.50 (m, 2 H), 4.16-4.22 (m, 4 H), 4.48 (dddd, *J* = 6.0, 6.0, 1.6, 1.6 Hz, 1 H), 4.57 (s, 2 H), 5.70-5.81 (m, 2 H), 7.24-7.43 (m, 11 H), 7.61-7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.1 (s'), 26.8 (q'), 40.5 (t'), 57.3 (t'), 61.7 (d'), 64.1 (t'), 71.5 (t'), 80.9 (s'), 87.0 (s'), 124.6 (d'), 127.6 (d'), 127.8 (d'), 128.0 (d'), 128.4 (d'), 129.6 (d'), 133.4 (d'), 133.6 (s') 135.5 (d'), 137.3 (s'); exact mass *m/z* calcd for $C_{15}H_{17}OSi$ (M-$C_{16}H_{19}O_2$) 241.1049, found 241.1043.

Methyl (*E*)-5-[[Dimethyl(1,1-dimethyl)ethylsilyl]oxy]-8-phenylmethoxy-2-octen-6-ynoate (41).

40 **41**

Imidazole (262.1 mg, 3.85 mmol) and *t*-$BuMe_2SiCl$ (377.2 mg, 2.50 mmol) were added consecutively to a stirred solution of **40** (527.5 mg, 1.93 mmol) in dry CH_2Cl_2 (60 mL). After 16 h, water (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 5:95 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 × 15 cm), using 5:95 EtOAc-hexane, gave **41** (688.7 mg, 92%) as a pure (^1H NMR, 200 MHz), colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.11 (s, 3 H), 0.15 (s, 3 H), 0.89 (s, 9 H), 2.57 (ddd, *J* = 7.1, 6.3, 1.4 Hz, 2 H), 3.70 (s, 3 H), 4.19 (d, *J* = 1.6 Hz, 2 H), 4.48-4.60 (m, 3 H; includes a singlet at δ 4.57, 2 H), 5.91 (dt, *J* = 15.7, 1.4 Hz, 1 H), 6.98 (dt, *J* = 15.7, 7.3 Hz, 1 H), 7.26-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -5.3 (q'), -4.7 (q'), 18.0 (s'), 25.5 (q'), 41.2 (t'), 51.1 (q'), 57.0 (t'), 61.6 (d'), 71.2 (t'), 80.8 (s'), 86.8 (s'), 123.6 (d'), 127.6 (d'), 127.8 (d'), 128.2 (d'), 137.3 (s'), 143.9 (d'), 166.3 (s').

(*E*)-5-[[Dimethyl(1,1-dimethyl)ethylsilyl]oxy]-8-phenyl-methoxy-2-octen-6-yn-1-ol (42).

41 **42**

DIBAL (1.0 M in hexanes, 3.98 mL, 3.98 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **41** (617.1 mg, 1.59 mmol) in dry CH_2Cl_2 (100 mL). After 4 h, MeOH (2 mL), $Na_2SO_4 \cdot 10H_2O$ (3 g), Celite (5 g), and water (1 mL) were added sequentially to the cold (-78 °C) solution. The cold bath was removed and the mixture was stirred for an additional 1 h, filtered through a pad (4 × 3 cm) of Celite, using CH_2Cl_2, and evaporated. Flash chromatography of the residue over silica gel (3.5 × 17 cm), using 3:7 EtOAc-hexane, gave **42** (462.6 mg, 81%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3406 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 3 H), 0.14 (s, 3 H), 0.90 (s, 9 H), 1.39 (s, 1 H), 2.38-2.48 (m, 2 H), 4.05-4.12 (m, 2 H), 4.19 (d, *J* = 1.6 Hz, 2 H), 4.36-4.48 (m, 1 H), 4.57 (s, 2 H), 5.69-5.79 (m, 2 H), 7.25-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -5.0 (q'), -4.5 (q'), 18.2 (s'), 25.7 (q'), 41.5 (t'), 57.3 (t'), 62.8 (d'), 63.5 (t'), 71.3 (t'), 80.4 (s'), 87.7 (s'), 127.7 (d'), 127.8 (d'), 128.0 (d'), 128.4 (d'), 132.4 (d'), 137.4 (s'); exact mass *m/z* calcd for $C_{17}H_{25}O_2Si$ (M-C_4H_7O) 289.1624, found 289.1626.

(2*R,3*R**,5*R**)- and (2*R**,3*R**,5*S**)-(±)-5-[[Dimethyl(1,1-dimethyl)ethylsilyl]oxy]-2,3-epoxy-8-phenylmethoxy-6-octyn-1-ol (43a,b).**

42 **43a,b**

m-CPBA (57-86%, 514 mg) was added in one lot to a stirred and cooled (0 °C) solution of **42** (407.8 mg, 1.13 mmol) in bench CH_2Cl_2 (40 mL). After 3 h, the cold bath was removed and saturated aqueous $NaHCO_3$ (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 until extraction was complete (TLC control, silica, 3:7 EtOAc-hexane), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 19 cm), using 3:7 EtOAc-hexane, gave epoxides **43a** and **43b** as an inseparable mixture of diastereomers (324.1 mg, 76%). The ratio of isomers was unknown; the relative intensities of the ^{13}C signals indicates one major and one minor isomer. The material had: FTIR (CH_2Cl_2 cast) 1724, 3397 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.14 (s, 3 H, δ 0.12 for minor isomer), 0.18 (s, 3 H, δ 0.16 for minor isomer), 0.92 (s, 9 H, δ 0.90 for minor isomer), 1.76-2.09 (m, 3 H), 2.92-3.04 (m, 1 H), 3.08-3.21 (m, 1 H), 3.62 (dd, *J* = 12.6, 4.3 Hz, 1 H), 3.90 (dd, *J* = 12.6, 2.7 Hz, 1 H), 4.13-4.22 (m, 2 H), 4.53-4.67 (m, 3 H, including a singlet at δ 4.56, 2 H), 7.25-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$,

50.3 MHz) (the ^{13}C signals indicated are for the major isomer) δ -5.1 (q'), -4.5 (q'), 18.2 (s'), 25.7 (q'), 40.9 (t'), 52.8 (d'), 57.3 (t'), 59.0 (d'), 60.3 (d'), 61.6 (t'), 71.5 (t'), 80.6 (s'), 87.4 (s') 127.9 (d'), 128.2 (d'), 128.4 (d'), 137.3 (s'); exact mass *m/z* calcd for $C_{17}H_{25}O_2Si$ ($M-C_4H_7O_2$) 289.1624, found 289.1623.

(2*R,3*R**,5*R**)- and (2*R**,3*R**,5*S**)-(±)-5-[[Dimethyl(1,1-dimethyl)ethylsilyl]oxy]-2,3-epoxy-8-phenylmethoxy-6-octynal (44a,b).**

43a,b **44a,b**

Molecular sieves (4Å, 88.6 mg) and pyridinium chlorochromate (266 mg, 1.23 mmol) were added consecutively to a stirred solution of **43a,b** (309.2 mg, 0.82 mmol) in dry CH_2Cl_2 (15 mL). After 10 h, the mixture was filtered through a pad (2 × 3 cm) of silica gel, using 1:1 EtOAc-hexane (TLC control, silica, 1:9 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 18 cm), using 1:9 EtOAc-hexane, gave aldehydes **44a,b** (190.3 mg, 62%) as a mixture of inseparable diastereomers: FTIR (CH_2Cl_2 cast) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.15 (s, 3 H), 0.18 (s, 3 H), 0.92 (s, 9 H), 1.82-2.16 (m, 2 H), 3.13-3.24 (m, 1 H), 3.37-3.49 (m, 1 H), 4.14-4.24 (m, 2 H), 4.55 (s, 2 H), 4.59-4.70 (m, 1 H), 7.25-7.39 (m, 5 H), 9.0

(d, J = 6.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) (the ^{13}C signals indicated are for the major isomer) δ -5.2 (q'), -4.6 (q'), 18.1 (s'), 25.7 (q'), 40.3 (t'), 55.6 (d'), 57.2 (t'), 59.3 (d'), 60.2 (d'), 71.6 (t'), 81.2 (s'), 86.6 (s'), 127.9 (d'), 128.0 (d'), 128.4 (d'), 137.3 (s'), 197.9 (d').

(2*R,3*R**,5*R**)- and (2*R**,3*R**,5*S**)-(±)-2,3-Epoxy-5-hydroxy-8-phenylmethoxy-6-octynal (45a,b).**

44a,b **45a,b**

Bu_4NF (1.0 M in THF, 0.98 mL, 0.98 mmol) was added dropwise to a stirred solution of **44a,b** (183.4 mg, 0.49 mmol) in dry THF (15 mL). After 3 h, water (15 mL) was added and the aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 2:3 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 14 cm), using 2:3 EtOAc-hexane, gave 107 mg of a mixture of compounds suspected to be **45a,b**. This mixture was used directly in the next step without characterization.

(2*R,3*R**,5*R**)- and (2*R**,3*R**,5*S**)-(±)-5-[[Bis(1,1-dimethyl)ethylsilyl]oxy]-2,3-epoxy-8-phenylmethoxy-6-octynal (46a,b).**

45a,b **46a,b**

Imidazole (66.7 mg, 0.98 mmol) and *t*-Bu_2SiHCl (0.14 mL, 0.69 mmol) were added consecutively to a stirred solution of **45a,b** (from the previous reaction) in dry THF (20 mL). After 12 h, water (20 mL) was added and the aqueous layer was extracted with EtOAc until extraction was complete (TLC control, silica, 1:9 EtOAc-hexane). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 16 cm), using 1:9 EtOAc-hexane, gave **46a,b** (140.1 mg, 71% over two steps) as an inseparable mixture of diastereomers: FTIR (CH_2Cl_2 cast) 1731, 2100 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 1.04 (s, 9 H), 1.07 (s, 9 H), 2.01-2.10 (m, 2 H), 3.23 (dt, *J* = 6.2, 2.0 Hz, 1 H), 3.46-3.57 (m, 1 H), 4.18 (s, 1 H), 4.22 (dd, *J* = 5.9, 1.6 Hz, 2 H), 4.57 (d, *J* = 5.4 Hz, 2 H), 4.70-4.82 (m, 1 H), 7.26-7.39 (m, 5 H), 9.04 (d, *J* = 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) (the ^{13}C signals indicated are for the major isomer) δ 19.7 (s'), 20.2 (s'), 27.3 (q'), 27.7 (q'), 40.2 (t'), 53.6 (d'), 57.3 (t'),

59.3 (d'), 63.5 (d'), 71.6 (t'), 82.3 (s'), 85.8 (s'), 127.9 (d'), 128.1 (d'), 128.5 (d'), 137.4 (s'), 198.0 (d'); exact mass *m/z* calcd for $C_{19}H_{25}O_4Si$ ($M-C_4H_9$) 345.1522, found 345.1518.

References and Footnotes

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